Synthesis and Biological Evaluation of Pyrroloindolines as Positive Allosteric Modulators of the α1β2γ2 $GABA_A$ Receptor

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Supporting Information

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1. Supplemental Tables and Figures

Table S1. Preliminary screen for functional effects of five pyrroloindoline compounds on Cys loop receptors. In this screen five pyrroloindoline compounds (Figure S1), were tested for modulation of seven pLGICs: muscle type nAChR, α4β2 nAChR, α7 nAChR, 5-HT_{3A} receptor, α1β2γ2 $GABA_A$ receptor, α1β2 $GABA_A$ receptor, GluR2, and the glycine receptor. Relative modulation of the current response as a result of co-application of endogenous agonist EC_{50} dose and 20-40 μM of compound. Table adapted from Daeffler, K.N.-M. 2014 and Marotta, C.B. 2015.[1,2] Values are expressed as mean ± SEM.

Receptor	AMAO-1 (%)	AMAO-1-71 (%)	(±)-2 (%)	AMAO-1-98 (%)	AMAO-1-100 (%)
Muscle (9')	-21 ± 1	-29 ± 3	-53 ± 3	-7 ± 3	-81 ± 6
A3B2 α4(L9'A)β2	-28 ± 2	-47 ± 4	-29 ± 6	-11 ± 2	-44 ± 2
A7 (T6'S)	-62 ± 4	-68 ± 7	-92 ± 4	-57 ± 10	-96 ± 3
5-HT_{3A}	-3 ± 2	-23 ± 4	-3 ± 5	3 ± 12	-11 ± 8
α1β2γ2 $GABA_A$	-27 ± 4	-27 ± 11	**52 ± 10**	-27 ± 21	10 ± 5
α1β2 $GABA_A$			**16 ± 2**		
GluR2	-6 ± 1	0 ± 2	-9 ± 6	-11 ± 5	-12 ± 5
Glycine	-6	-9 ± 9	3 ± 7	18 ± 10	-16 ± 6

Table S2. Relative modulation of GABA EC_{50} responses in WT $GABA_A$ receptors. Values are expressed as mean ± SEM.

Subtype	Ligand	Relative modulation of GABA EC_{50} (%)	N	$\lvert I_{max} \rvert$ (μA)
α1β2γ2	GABA only	-0.3 ± 1.6	20	0.49 – 7.7
α1β2γ2	0.08% DMSO	-5.5 ± 2.2	8	1.3 - 33
α1β2γ2	(±)-2	17 ± 4.0	14	0.11 – 9.9
α1β2γ2	(-)-2	-3.7 ± 3.7	19	0.31 – 10
α1β2γ2	(+)-2	16 ± 4.1	14	3.7 – 14
α1β2	(±)-2	28 ± 5.2	10	0.80 – 9.3
α1β2	(-)-2	9.2 ± 1.1	11	0.30 – 2.3
α1β2	(+)-2	17 ± 2.6	13	0.44 – 3.3

Table S3. EC_{50} values of (+)-2, GABA, and GABA co-application with (±)-2, (–)-11 or (+)-13. Values are expressed as mean ± SEM.

Subtype	Compound	EC_{50} (μM)	ΔEC_{50} (μM)	n_H	N	$\lvert I_{max} \rvert$ (μA)
α1β2γ2	(+)-2	110 ± 4.9	NA	2.6 ± 0.3	16	0.91 - 20
α1β2γ2	GABA	23 ± 0.45	0	1.3 ± 0.03	40	1.7 - 9.8
α1β2γ2	GABA + (±)-2	9.9 ± 0.48	13	1.7 ± 0.1	22	6.1 – 16
α1β2γ2	GABA + (-)-11	14 ± 1.1	9	0.98 ± 0.08	15	1.0 – 30
α1β2γ2	GABA + (+)-13	6.9 ± 0.44	16	1.4 ± 0.1	16	6.1 – 26

Table S4. Relative modulation of GABA EC_{10} responses by (±)-2 in α1β2γ2 mutant receptors. Values are expressed as mean ± SEM.

Mutant	Relative modulation of GABA EC_{10} (%)	N	$\lvert I_{max} \rvert$ (μA)
α1β2γ2 WT	62 ± 6.1	18	0.77 – 4.4
α1(H129R)β2γ2	88 ± 8.1	11	0.026 – 0.77
α1(Y209Q)β2γ2	86 ± 8.9	8	0.18 -2.3
α1β2(Q88C)γ2	69 ± 5.8	10	0.11 – 3.7
α1(S297I)β2(N289I)γ2(S319I)	1.1 ± 3.0	12	0.12 – 1.7
α1(S297I)β2γ2	41 ± 3.7	12	0.086 – 2.4
α1β2(N289I)γ2	9.7 ± 2.1	12	1.2 – 5.3
α1β2γ2(S319I)	66 ± 4.7	10	0.10 – 0.99
α1(S297I)β2(N289I)γ2	9.2 ± 2.0	12	0.36 – 2.5
α1β2 WT	38 ± 4.7	9	0.12 – 1.9
α1(S297I)β2(N289I)	-3.3 ± 13	11	0.032 – 0.84
α1(S297I)β2	16 ± 5.1	9	0.092 – 4.5
α1β2(N289I)	24 ± 16	8	0.046 – 1.2

Table S5. GABA EC_{50} values of $GABA_A$ WT and mutant receptors. Values are expressed as mean ± SEM.

Mutant	EC_{50} (μM)	n_H	N	$\lvert I_{max} \rvert$(μA)
α1β2γ2 WT	23 ± 0.45	1.3 ± 0.03	40	1.7 - 9.8
α1β2 WT	3.0 ± 0.072	1.5 ± 0.05	7	5.8 - 25
α1(H129R)β2γ2	16 ± 0.47	1.7 ± 0.06	17	0.37 – 4.0
α1(Y209Q)β2γ2	22 ± 0.81	1.6 ± 0.08	6	4.2 - 8.6
α1β2(Q88C)γ2	27 ± 1.8	1.4 ± 0.1	6	0.93 – 8.0
α1(S297I)β2(N289I)γ2(S319I)	0.53 ± 0.010	1.8 ± 0.05	13	3.5 – 6.4
α1(S297I)β2γ2	0.74 ± 0.021	1.8 ± 0.08	19	1.1 - 25
α1β2(N289I) γ2	27 ± 0.59	1.8 ± 0.06	11	0.04 - 17
α1β2γ2(S319I)	20 ± 0.65	1.7 ± 0.08	6	0.051 – 4.3
α1(S297I)β2(N289I)γ2	1.0 ± 0.028	2.0 ± 0.09	11	2.9 - 19
α1(S297I)β2	0.078 ± 0.0018	2.1 ± 0.09	20	0.071 – 4.3
α1β2(N289I)	2.8 ± 0.075	1.4 ± 0.05	10	1.0 – 3.7
α1(S297I)β2(N289I)	0.057 ± 0.0022	2.2 ± 0.2	7	0.59 – 4.8

Table S6. Relative modulation of GABA EC_{10} responses of the α1β2γ2 subtype by pyrroloindoline derivatives. Values are expressed as mean ± SEM.

Ligand	R_{C3}	R_{N1}	R_{C5}	R_{C2}	Relative modulation of GABA EC_{10} (%)	N	$\lvert I_{max} \rvert$ (μA)
(±)-2	OH	Me	H	Ph	62 ± 6.1	18	0.77 – 4.8
(-)-2	OH	Me	H	Ph	11 ± 2.2	8	2.1 – 3.6
(+)-2	OH	Me	H	Ph	130 ± 15	12	0.47 – 6.0
(-)-7	OH	NH	H	Ph	1.8 ± 1.7	14	0.76 – 5.2
(+)-7	OH	NH	H	Ph	41 ± 3.0	15	0.38 – 11

(-)-6	OH	Cbz	H	Ph	25	±	4.1	14	0.84 – 7.8
(+)-6	OH	Cbz	H	Ph	9.6	±	5.2	14	0.36 – 9.7
(-)-10	OMe	Me	H	Ph	24	±	2.2	6	0.43-1.2
(+)-10	OMe	Me	H	Ph	21	±	3.0	5	0.54-0.84
(-)-9	F	Me	H	Ph	27	±	3.0	11	0.73 – 8.3
(+)-9	F	Me	H	Ph	100	±	11	16	0.89 – 11
(-)-14	OH	Me	OMe	Ph	15	±	4.6	13	0.48 – 3.7
(+)-14	OH	Me	OMe	Ph	17	±	3.2	13	0.73 – 13
(-)-15	OH	Me	Morpholine	Ph	21	±	2.9	11	1.2 – 4.9
(+)-15	OH	Me	Morpholine	Ph	-4.8	±	1.8	12	0.89 – 8.7
(-)-12	OH	Me	CF_3	Ph	1.3	±	1.2	16	0.58 – 6.6
(+)-12	OH	Me	CF_3	Ph	110	±	9.5	16	0.87 – 12
(-)-13	OH	Me	Br	Ph	31	±	3.0	10	0.32 – 3.4
(+)-13	OH	Me	Br	Ph	210	±	21	12	2.3 – 19
(-)-11	OH	Me	I	Ph	230	±	24	16	2.2 – 6.2
(+)-11	OH	Me	I	Ph	35	±	5.6	15	0.45 – 3.9
(±)-SI-5	OH	Me	H	4-OMe-Ph	-2.9*	±	1.6	20	0.082 – 11
(-)-16	OH	Me	H	4-Br-Ph	160	±	11	13	0.63 – 6.8
(+)-16	OH	Me	H	4-Br-Ph	98	±	8.3	15	1.1 – 5.6

* relative modulation of GABA EC_{50}.

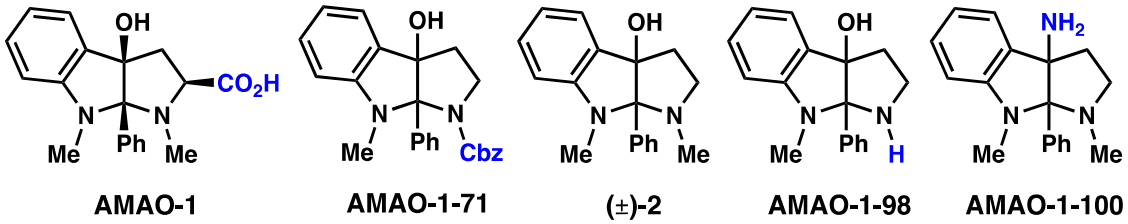


Figure S1. Pyrroloindoline compounds used in preliminary screen.

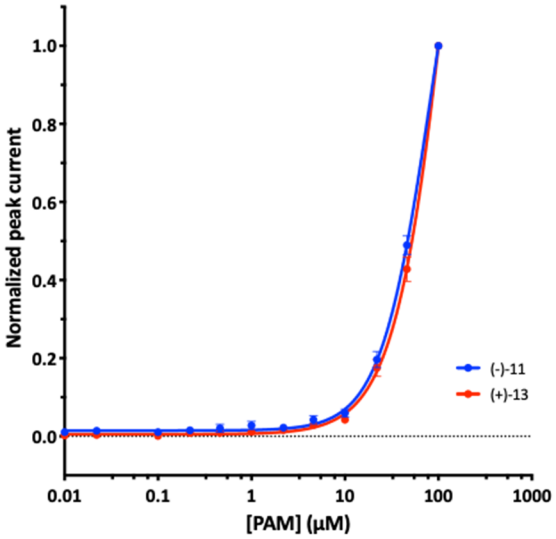


Figure S2. PAM EC_{50} of pyrroloindolines (-)-11 and (+)-13 at the α1β2γ2 $GABA_A$ receptor. All PAM doses are co-applied with GABA EC_5 doses.

2. Biological Evaluation Experimental Procedures

Molecular biology

Circular DNA of human $GABA_A$ receptor α1, β2s and γ2s subunits were in a pGEMhe plasmid. For both β2s and γ2s only the short isoforms were used, however for convenience we refer to the subunits as β2 and γ2. Site-directed mutagenesis was performed using the QuickChange protocol (Agilent Stratagene). cDNA in pGEMhe was linearized with restriction enzyme NheI (for α1 and γ2 subunits), and Sph1 (for the β2 subunit) (New England Biolabs). Purified linear DNA (Qiaquick PCR Purification kit, Qiagen) was then transcribed *in vitro* using the T7 mMessage Machine kit (Ambion). The resulting mRNA was isolated using the RNeasy RNA purification kit (Qiagen) and quantified by UV-vis spectroscopy (NanoDrop 2000, ThermoFisher Scientific). cDNA and mRNA were stored at -20˚C and -80˚C respectively.

Oocyte preparation and mRNA injection

Xenopus laevis oocytes (stage V-VI) were harvested and injected with mRNA according to previously described protocols.[3] Oocytes were injected with 50-75 nl mRNA in nuclease-free water. Post injection, oocytes were incubated at 18˚C in ND96 solution (96 mM NaCl, 2mM KCl, 1mM $MgCl_2$, 1.8 mM $CaCl_2$, 5 mM HEPES, pH 7.5) supplemented with 0.05 mg/ml gentamycin (Sigma), 2.5 mM sodium pyruvate (Acros Organics), and 0.67 mM theophylline (Sigma).

For expression of wild-type α1β2γ2 receptors, α1, β2, and γ2 mRNA were mixed in 2:2:1 ratio by mass. For expression of wild-type α1β2 receptors, α1 and β2 mRNA were mixed in 1:1 ratio by mass. Each cell was injected with 5 ng or 15 ng mRNA in a single injection for the α1β2γ2 and α1β2, respectively. Oocytes were then incubated for 24 h before recording. Proper injection ratios for mutant receptors were determined after analysis of the dose-response curve and optimized when necessary. All ECD mutant receptors and the triple TMD mutant were injected with a 2:2:1 ratio. Injection ratios for the TMD mutants were as follows: αMβγ and αMβMγ: 2:2:1; αβMγ: 2:10:1; αβγM: 1:1:8; αMβ, αβM and αMβM: 1:1.

Electrophysiology

All electrophysiological recordings were performed using the OpusXpress 6000A (Axon Instruments) in two-electrode voltage clamp mode at ambient temperature (20-25˚C). Oocytes were impaled with borosilicate glass pipettes filled with 3 M KCl (R = 0.3-3.0 MΩ) and clamped at a holding potential of -60 mV. ND96 solution with Ca^{2+} was used as running buffer. GABA and test-ligand solutions were prepared in ND96 with Ca^{2+} and 1 mL was applied over 15 s followed by a 5 min washout with buffer at a rate of 3 mL min^{-1} (chamber volume, 500 μL). Data for each condition were obtained from at least two different batches of oocytes. Data were sampled at 50 Hz.

For potentiation experiments an adapted protocol, previously described by Marotta 2015, was used.[2] The protocol is as follows: three identical GABA doses were applied,

followed by a dose of the test-ligand at 40 μM. After a 30 s incubation period, a test dose was applied containing both GABA and the test-ligand. Finally, two doses of GABA were applied. The first test dose evaluates agonism properties, the second dose tests for modulation of the GABA response, which can be potentiating or inhibiting. The first three GABA doses aim to establish a baseline of the GABA response at that concentration, and the purpose of the last two GABA doses is to verify proper functioning of the receptor post modulation and control for independent rise in current amplitude. Dose-response measurements were performed using a series of ~2-fold concentration steps, spanning multiple orders of magnitude, for a total of 8-24 doses.

Two-electrode voltage-clamp traces were processed in Clampfit 10.3 (Axon Instruments). Raw traces were filtered using a low pass Gaussian filter at 5 Hz, followed by a subtraction of the average baseline current preceding ligand application. For potentiation experiments the current responses from the five GABA doses were averaged (GABA only) and subtracting this from the response of the co-application dose (GABA + test-ligand) gave the calculated change in response. Multiplying this value by 100% rendered the relative modulation (inhibition/potentiation) of the GABA response by the test-ligand. Relative modulation is reported as the mean ± standard error of the mean (SEM). For the GABA concentration either the EC_{50} or EC_{10} was used as specified in the results section. For dose-response experiments, normalized peak currents were averaged and fit to the Hill equation, $I_{norm} = 1/(1 + (EC_{50}/[\text{agonist}]^{nH})$ in Prism 8 (GraphPad Software, Inc.), where I_{norm} is the normalized peak current at a given agonist concentration, EC_{50} is the agonist concentration that elicits a half-maximum response, and n_H is the Hill coefficient. Peak currents were normalized to the maximum current observed for that cell. Unless otherwise stated, EC_{50} and n_H data are shown as mean ± standard error of the mean (SEM). Geometry calculations were performed in Spartan 14 v1.1.9.

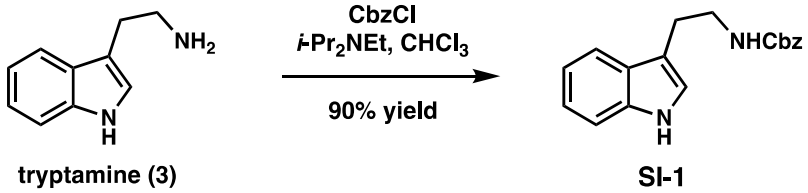
3. Materials and Methods Synthetic Chemistry

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), toluene (PhMe), tetrahydrofuran (THF), and 1,4-dioxane were dried by passing through activated alumina columns. Triethylamine (Et_3N) and *N,N*-diisopropylethylamine (*i*-Pr_2NEt) were distilled over calcium hydride prior to use. 3Å molecular sieve pellets were flame-dried under high vacuum prior to use. *N*-chlorosuccinimide was purified by recrystallization from AcOH and *N*-bromosuccinimide was purified by recrystallization from water prior to use. All other commercially obtained reagents were used as received unless specifically indicated. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV and/or $KMnO_4$ staining. Silica gel column chromatography was performed as described by Still *et al.* using silica gel (230–400 mesh) purchased from Silicycle.[4] ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz respectively) or a Bruker Avance III HD with Prodigy cyroprobe (at 400 MHz and 101 MHz respectively). NMR data is reported relative to internal chloroform or acetonitrile solvent peaks (with respect to TMS (tetramethylsilane)): $CDCl_3$, ^1H, δ = 7.26, ^{13}C, δ = 77.16; CD_3CN, ^1H, δ = 1.94, ^{13}C, δ = 118.26). ^{19}F spectra were recorded on a Varian 300 MHz spectrometer. NMR data are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. HRMS, analytical SFC, and preparative chiral resolution experiments were performed at the Caltech Center for Catalysis and Chemical Synthesis. HRMS data were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source using electrospray ionization (ESI). Analytical chiral SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system (CO_2 = 1450 psi, column temperature = 40 °C) with a Chiralpak AD-H column (4.6 mm x 25 cm). Preparative chiral resolution of pyrroloindoline (±)-**2** was achieved using an Agilent 1200 series HPLC with a 20 x 250 mm 5 μm Daicel IC chiral preparative HPLC column. Preparative chiral resolution of carbamate (±)-**6** and bromocarbamate (±)-**SI-3** were achieved using a Jasco 2000 series preparative SFC system with a 21.2 x 250 mm 5 μm AD-H column.

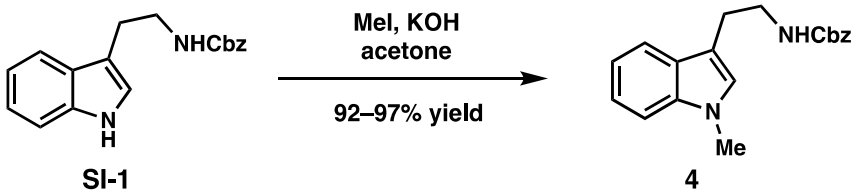
Abbreviations used: Et_2O – diethyl ether; PhMe – toluene; EtOAc – ethyl acetate; THF – tetrahydrofuran; Et_3N – triethylamine; *i*-Pr_2NEt – *N,N*-diisopropylethylamine.

4. Experimental Procedures for Preparation of Pyrroloindolines

Synthesis of the Pyrroloindoline Core

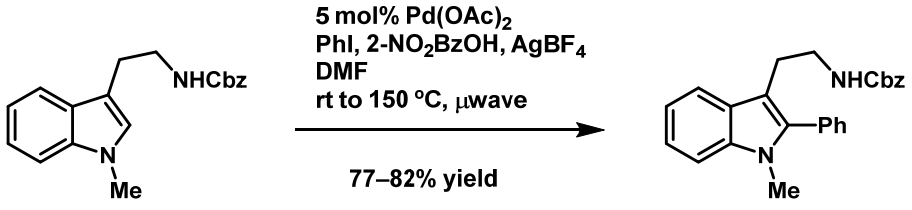


A flame-dried 100 mL round-bottom flask was charged with tryptamine (2.0 g, 12.48 mmol) and chloroform (20 mL). Then *i*-Pr_2NEt (4.4 mL, 25.34 mmol, 2.03 equiv) and benzyl chloroformate (2.0 mL, 14.11 mmol, 1.13 equiv) were added dropwise via syringe successively. After stirring at ambient temperature for 1 h, water was added (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL x 2) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was dry-loaded with Celite and purified by silica gel chromatography (10–66% EtOAc/hexanes) to afford **SI-1** (3.3 g, 90% yield) as a slightly pink off-white solid. The spectral data were in agreement with those reported in the literature.[5]



A flame-dried 100 mL round-bottom flask was charged with **SI-1** (1.5 g, 5.10 mmol) and acetone (21 mL). Potassium hydroxide (1.43 g, 25.48 mmol, 5.0 equiv) was ground with a mortar and pestle to a fine powder and added to the reaction, which was then stirred vigorously for 10 min. To the yellow-orange suspension was added methyl iodide (0.35 mL, 5.61 mmol, 1.1 equiv) dropwise via syringe. After stirring for 1 h, a second portion of potassium hydroxide (1.43 g, 25.48 mmol, 5.0 equiv) ground with a mortar and pestle to a fine powder was added to the reaction, followed by a second charge of methyl iodide (0.35 mL, 5.61 mmol, 1.1 equiv) dropwise via syringe. The suspension was stirred for 1 h. Water (12 mL) was added and the reaction was stirred for an additional 15 min. The acetone was removed by rotary evaporation. Saturated aqueous NaCl (3 mL) was added and the solution was extracted with CH_2Cl_2 (20 mL x 4). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was

purified by silica gel chromatography (10–33% EtOAc/hexanes) to afford **4** (1.60 g, 95% yield) as a viscous yellow oil. The spectral data were in agreement with those reported in the literature.[6]



4 **5**

On a benchtop, two 10–20 mL microwave vials were each charged with **4** (650 mg, 2.11 mmol), DMF (8.5 mL), 2-nitrobenzoic acid (528 mg, 3.16 mmol, 1.5 equiv), iodobenzene (0.95 mL, 8.43 mmol, 4.0 equiv), $Pd(OAc)_2$ (24 mg, 0.11 mmol, 0.05 equiv), and then $AgBF_4$ (615 mg, 3.16 mmol, 1.5 equiv). A magnetic vane stirbar was added and the reactions were flushed with argon and capped using a microwave vial crimper. The mixtures were then stirred vigorously (660 rpm) in the dark for 40 min at ambient temperature. The black-brown opaque solutions were then subjected to microwave irradiation using a Biotage microwave reactor at 150 °C for 4 min (stirring at 660 rpm). The reactions were each filtered through a small plug of Celite, eluting with EtOAc (30 mL). The filtrates were combined and washed with saturated aqueous NH_4Cl (25 mL x 2), saturated aqueous $NaHCO_3$ (25 mL x 2), and brine (25 mL x 2). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (5–25% EtOAc/hexanes) to afford **5** (1.251 g, 77% yield) as a viscous reddish yellow oil.

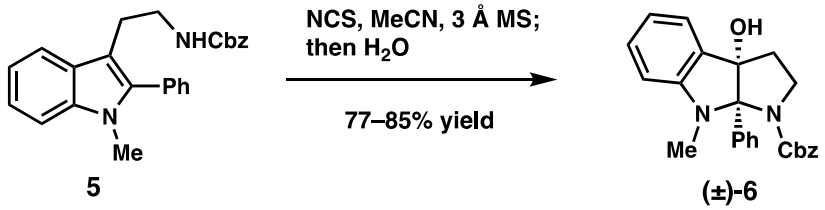
TLC R_f = 0.47 in 25% EtOAc/hexanes (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$, compound exists as a 6:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) δ 7.68 (d, *J* = 7.9 Hz, 1H*), 7.54 (br s, 1H§), 7.50 – 7.41 (m, 3H*, 3H§), 7.40 – 7.26 (m, 9H*, 9H§), 7.17 (t, *J* = 7.4 Hz, 1H*), 7.12 (br s, 1H§), 5.04 (s, 2H*, 2H§), 4.74 (t, *J* = 6.8 Hz, 1H*), 4.53 (br s, 1H§), 3.59 (s, 3H*, 3H§), 3.44 (td, *J* = 6.7, 6.7 Hz, 2H*), 3.38 (br s, 2H§), 2.94 (t, *J* = 6.9 Hz, 2H*), 2.90 (br s, 2H§) ppm.

^{13}C NMR (101 MHz, $CDCl_3$; compound exists as a 6:1 mixture of rotamers, only the major rotamer is reported) δ 156.3, 139.0, 137.2, 131.8, 130.7, 128.7, 128.6, 128.4, 128.1, 122.0, 119.6, 119.0, 109.6, 66.5, 41.8, 30.9, 25.2 ppm.

FTIR (NaCl/thin film): 3413, 3339, 3055, 3030, 2940, 1718, 1701, 1511, 1368, 1361, 1334, 1233, 1132 cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{25}H_{25}N_2O_2$ $[M+H]^+$: 385.1911, found: 385.1924.



5 **(±)-6**

A flame-dried 100 mL round-bottom flask was charged with **5** (900 mg, 2.34 mmol), MeCN (23 mL), and 3Å molecular sieve pellets (1.2 g, 1.3 x mass of **5**). A solution of *N*-chlorosuccinimide (319 mg, 2.39 mmol, 1.02 equiv) in MeCN (47 mL) was added dropwise over 10 min. The flask was wrapped in aluminum foil and stirred in the dark for 3.5 h. TLC analysis indicated consumption of starting material (R_f of the putative chloride intermediate = 0.56; 25% EtOAc/hexanes, UV, $KMnO_4$). Water (47 mL) was then added dropwise and the reaction was stirred for 1 h. The reaction mixture was filtered through a Celite pad and rinsed copiously with EtOAc. A 2:1 mixture of saturated aqueous $NaHCO_3$/brine (20 mL) was added and the layers were separated in a separatory funnel. The aqueous layer was extracted with EtOAc (25 mL x 3) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10–30% EtOAc/hexanes) to afford (±)-**6** (845 mg, 85% yield) as a yellow orange foam.

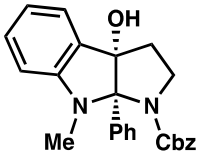
TLC R_f = 0.32 in 25% EtOAc/hexanes (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$, compound exists as a 1.1:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) δ 7.48 – 7.09 (m, 11H*, 11H§), 6.78 (td, *J* = 7.4, 1.7 Hz, 2H*), 6.75 – 6.68 (m, 2H§), 6.58 (d, *J* = 7.8 Hz, 1H*), 6.50 (d, *J* = 7.9 Hz, 1H§), 5.12 (d, *J* = 12.4 Hz, 1H*), 5.05 (s, 1H*), 5.02 (s, 1H§), 4.85 (d, *J* = 12.4 Hz, 1H§), 4.05 (dd, *J* = 10.8, 8.5 Hz, 1H§), 3.98 (ddd, *J* = 10.5, 8.4, 1.8 Hz, 1H*), 3.30 (td, *J* = 11.1, 6.2 Hz, 1H*), 3.21 (td, *J* = 11.4, 5.9 Hz, 1H§), 3.04 (s, 3H*), 2.76 (s, 3H§), 2.55 – 2.36 (m, 2H*), 2.33 – 2.13 (m, 2H§), 1.44 (br s, 1H*, 1H§) ppm.

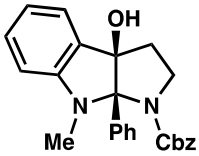
^{13}C NMR (101 MHz, $CDCl_3$; compound exists as a 1.1:1 mixture of rotamers) δ 155.1, 154.6, 151.3, 151.1, 136.8, 135.7, 130.9, 128.8, 128.6, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.52, 127.46, 123.79, 123.76, 118.3, 118.0, 106.7, 106.6, 94.4, 93.7, 89.8, 88.7, 67.1, 66.9, 46.5, 46.3, 34.3, 33.8, 32.0, 31.4 ppm.

FTIR (NaCl/thin film): 3049, 3056, 3032, 2945, 2891, 1695, 1684, 1675, 1609, 1491, 1401, 1348, 1186, 1117, 1004 cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{25}H_{25}N_2O_3$ $[M+H]^+$: 401.1860, found: 401.1877.



(+)-6



(–)-6

Preparative chiral SFC resolution: Carbamate (±)-**6** (219 mg) was dissolved in a minimal amount of *i*-PrOH (~4 mL). This solution of racemic compound was resolved by preparative chiral SFC, serially injecting 200 µL at a time (isocratic: 40% *i*-PrOH /CO_2) to afford (–)-**6** (92 mg) and (+)-**6** (85 mg) as yellow foams.

(+)-6:

[α]$_D^{25}$ = +437.3° (c =0.975, $CHCl_3$).

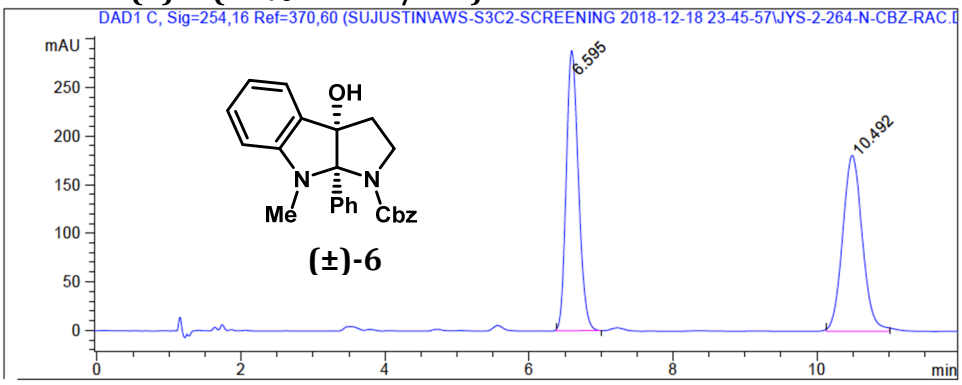
SFC: >99% ee (AD-H column: 12 min, 30% *i*-PrOH/CO_2; retention time = 10.4 min).

(–)-6:

[α]$_D^{25}$ = –407.4° (c = 0.995, $CHCl_3$).

SFC: >99% ee (AD-H column: 12 min, 30% *i*-PrOH/CO_2; retention time = 6.6 min).

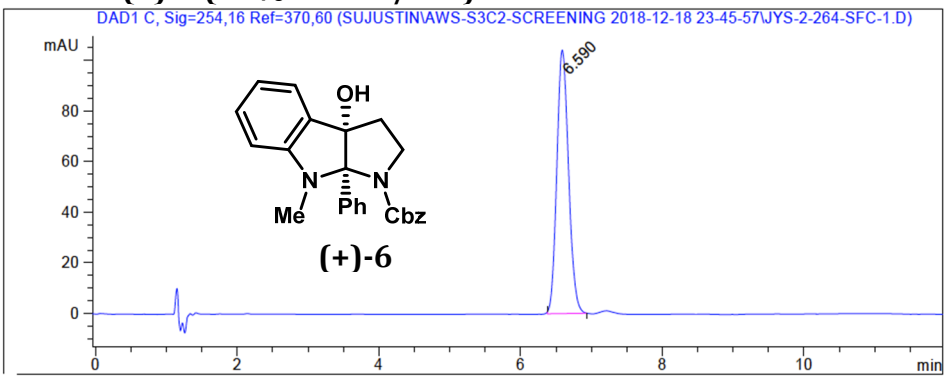
Chiral SFC trace of (±)-6 (30% *i*-PrOH/CO_2):



(±)-6

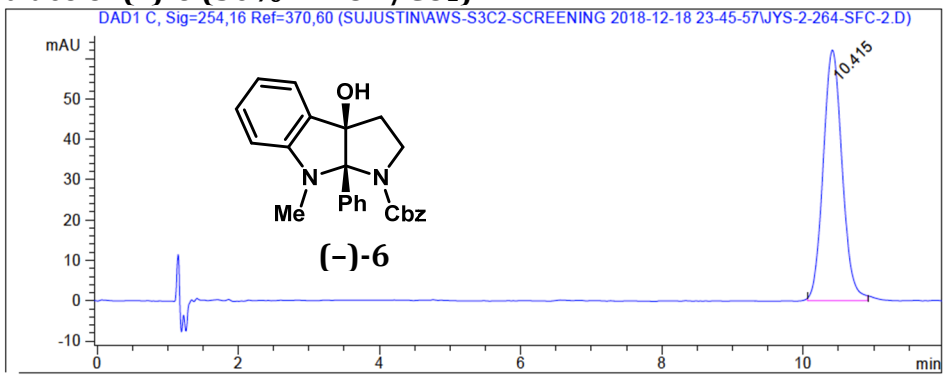
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.595	BB	0.1811	3384.83936	288.08844	49.6548
2	10.492	BB	0.2935	3431.90869	180.79875	50.3452

Chiral SFC trace of (+)-6 (30% *i*-PrOH/CO_2):

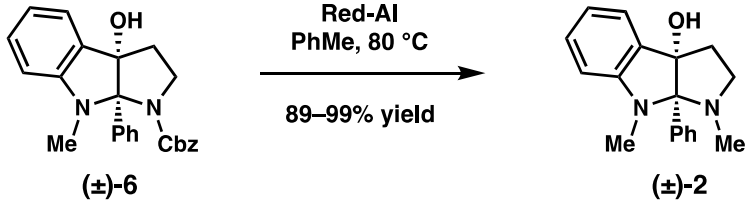


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.590	BB	0.1782	1196.15979	103.96140	100.0000

Chiral SFC trace of (–)-6 (30% *i*-PrOH/CO_2):



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.415	BB	0.2896	1158.81091	62.11673	100.0000



A flame-dried 50 mL round-bottom flask was charged with (±)-**6** (500 mg, 1.25 mmol) and PhMe (25 mL). Red-Al (60 wt% in PhMe, 3.25 mL, 9.99 mmol, 8.0 equiv) was added dropwise. Gas evolution was observed during the addition. After stirring for 5 min, the flask was flushed with argon, sealed, and the reaction was stirred at 80 °C for 2.5 h. The reaction was cooled to room temperature and then slowly quenched with a 1 M aqueous solution of Rochelle's salt (6.5 mL). The resulting mixture was stirred for 1 h and then extracted with Et_2O (15 mL x 4). The combined organic extracts were dried ($MgSO_4$), filtered, and

concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10–20% EtOAc/hexanes) to afford (±)-**2** (340 mg, 97% yield) as a yellow solid.

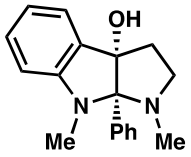
TLC R_f = 0.27 in 33% EtOAc/hexanes (UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.35 (br s, 2H), 7.32 (tt, *J* = 7.2, 1.4 Hz, 1H), 7.28 – 7.19 (m, 2H), 6.71 (td, *J* = 7.3, 1.0 Hz, 1H), 6.43 (d, *J* = 7.8, 1H), 3.03 (ddd, *J* = 9.1, 5.0, 2.8 Hz, 1H), 2.77 (s, 3H), 2.66 – 2.53 (m, 1H), 2.48 (s, 3H), 2.33 – 2.19 (m, 2H), 1.39 (br s, 1H) ppm. Note: A total of 7H aromatic protons observed with relaxation delay = 1 sec; 9H expected if relaxation delay is > 5 sec.

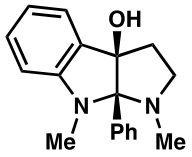
^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 137.5, 130.9, 130.0, 128.9, 128.2, 124.1, 117.0, 110.1, 104.1, 98.4, 90.8, 51.6, 40.7, 36.7, 34.5 ppm.

FTIR (NaCl/thin film): 3540, 3435, 3051, 2931, 2791, 1608, 1492, 1473, 1445, 1370, 1308, 1106, 1028 cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{18}H_{21}N_2O$ $[M+H]^+$: 281.1648, found: 281.1655.



(+)-2



(–)-2

Preparative chiral HPLC resolution: Pyrroloindoline (±)-**2** (187 mg) was dissolved in 15 mL of 9:1 hexanes/IPA. This solution of racemic compound was resolved using preparative chiral HPLC, injecting serially 260 μL at a time (isocratic: 4% *i*-PrOH/hexanes) to afford (–)-**2** (88 mg) and (+)-**2** (85 mg) as light yellow solids.

(+)-**2:**

$[\alpha]_D^{25}$ = +26.4° (c = 1.00, $CHCl_3$).

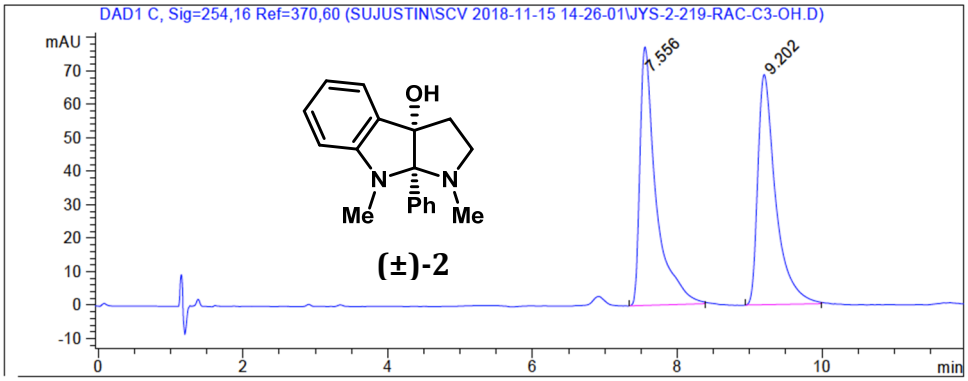
SFC: 98.4% ee (AD-H column: 12 min, 15% *i*-PrOH/CO_2; retention time = 6.9 min).

(–)-2:

$[\alpha]_D^{25}$ = –26.6° (c = 1.00, $CHCl_3$).

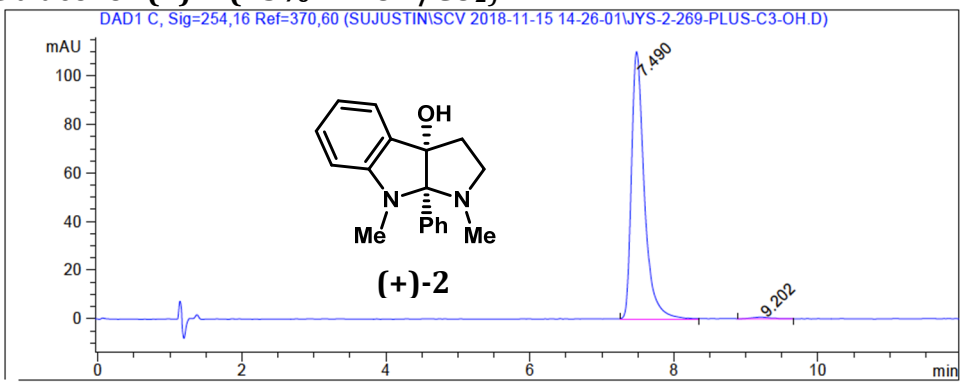
SFC: >99% ee (AD-H column: 12 min, 15% *i*-PrOH/CO_2; retention time = 8.4 min).

Chiral SFC trace for (±)-2 (15% *i*-PrOH/CO_2):



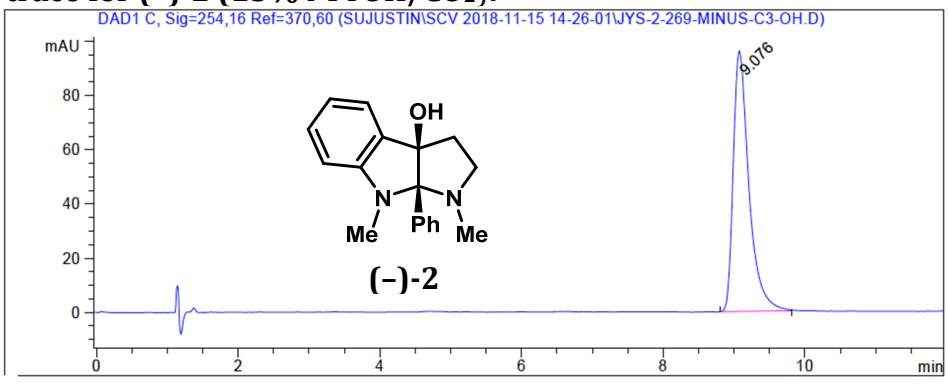
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.556	BB	0.2252	1200.38086	77.30421	50.3719
2	9.202	BB	0.2545	1182.65710	68.83022	49.6281

Chiral SFC trace for (+)-2 (15% *i*-PrOH/CO_2):



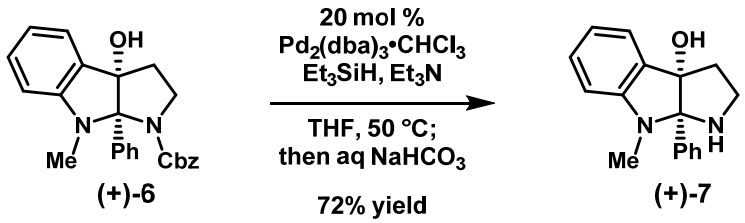
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.490	BB	0.1964	1367.62573	107.52038	98.9857
2	9.202	BB	0.2948	14.01365	7.08409e-1	1.0143

Chiral SFC trace for (–)-2 (15% *i*-PrOH/CO_2):

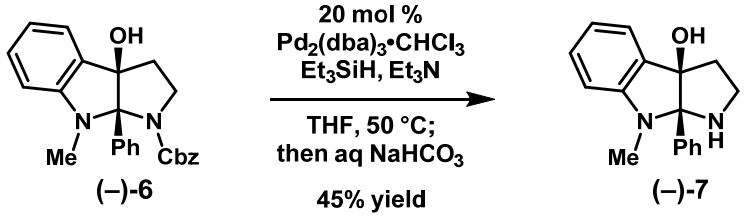


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.076	BB	0.2310	1475.53369	96.19193	100.0000

Derivatization of the Pyrroloindoline Framework



A 25 mL round-bottom flask containing (+)-**6** (27 mg, 67 μmol) was charged with THF (1.9 mL), Et_3SiH (430 μL, 2.7 mmol, 40 equiv), Et_3N (20 μL, 135 μmol, 2.0 equiv), and $Pd_2(dba)_3$•$CHCl_3$ (14 mg, 130 μmol, 0.2 equiv). The flask was sealed under argon, wrapped in aluminum foil, and heated to 50 °C. After stirring for 18 h, the dark purple red solution was cooled to room temperature. Saturated aqueous $NaHCO_3$ (2 mL) was then added and the solution was stirred at 23 °C for 5 h. The white suspension was then extracted with EtOAc (5 mL x 4) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10–40% EtOAc/hexanes) to afford (+)-**7** (13.0 mg, 72% yield) as a white solid.



The same procedure was performed on (–)-**6** (30 mg, 75 μmol) to afford (–)-**7** (9.0 mg, 45% yield) as a white solid.

(+)-7:

$[\alpha]_D^{25}$ = +54.6° (c = 0.65, MeOH).

SFC: >99% ee (AD-H column: 12 min, 30% *i*-PrOH/CO_2; retention time = 7.6 min).

(–)-7:

$[\alpha]_D^{25}$ = –53.2° (c = 0.45, MeOH).

SFC: >99% ee (AD-H column: 12 min, 30% *i*-PrOH/CO_2; retention time = 6.8 min).

TLC R_f = 0.19 in 33% EtOAc/hexanes (UV, $KMnO_4$).

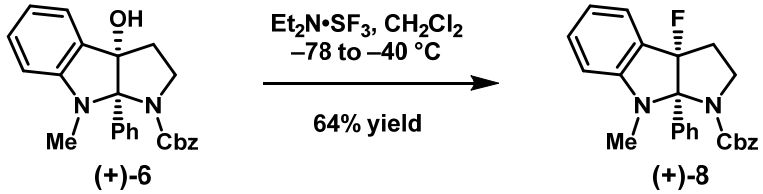
^{1}H NMR (400 MHz, CD_3CN) δ 7.45 – 7.38 (m, 2H), 7.34 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 2H), 7.30 – 7.24 (m, 1H), 7.17 – 7.11 (m, 2H), 6.62 (td, *J* = 7.4, 1.0 Hz, 1H), 6.42 (dd, *J* = 8.2, 1.0 Hz, 1H), 3.14 (ddd, *J* = 9.5, 5.1, 3.5 Hz, 1H), 2.68 (td, *J* = 9.4, 7.8 Hz, 1H), 2.64 (br s, 1H), 2.57 (s, 3H),

2.23 – 2.10 (m, 2H) ppm. Note: One of the *N*–H/*O*–H protons was not observed under these conditions.

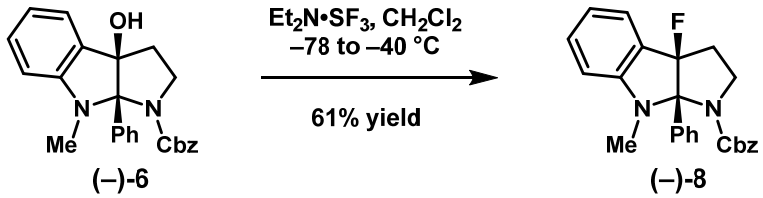
^{13}C NMR (101 MHz, CD_3CN) δ 152.7, 140.9, 132.4, 130.5, 128.9, 128.8, 128.3, 124.7, 117.3, 105.1, 95.2, 90.4, 43.8, 42.9, 28.6 ppm.

FTIR 3307, 3053, 2930, 2857, 1608, 1494, 1371, 1306, 1206, 1121, 1058, 1016 (NaCl/thin film): cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{17}H_{19}N_2O$ $[M+H]^+$: 267.1492, found: 267.1495.



A flame-dried 25 mL round-bottom flask was charged with (+)-**6** (30 mg, 75 μmol) and CH_2Cl_2 (2.0 mL). The solution was cooled to –78 °C and a solution of $Et_2N{\bullet}SF_3$ (30 μL, 225 μmol, 3.0 equiv) in CH_2Cl_2 (0.5 mL) was added dropwise and then stirred for 1 h. The reaction was allowed to warm to –40 °C and stirred for an additional 1 h. The reaction was then slowly quenched at this temperature with saturated aqueous $NaHCO_3$ (3 mL). The resulting mixture was extracted with CH_2Cl_2 (4 mL x 3) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10–25% EtOAc/hexanes) to afford (+)-**8** (19 mg, 64% yield) as a yellow viscous oil.



The same procedure was performed on (–)-**6** (17 mg, 61 μmol) to afford (–)-**8** (18 mg, 61% yield) as a yellow viscous oil.

(+)-8:

$[\alpha]_D^{25}$ = +416.1° (c = 0.63, $CHCl_3$).

SFC: >99% ee (AD-H column: 12 min, 20% *i*-PrOH/CO_2; retention time = 8.0 min).

(–)-8:

$[\alpha]_D^{25}$ = –429.7° (c = 0.65, $CHCl_3$).

SFC: >99% ee (AD-H column: 12 min, 20% *i*-PrOH/CO_2; retention time = 11.1 min).

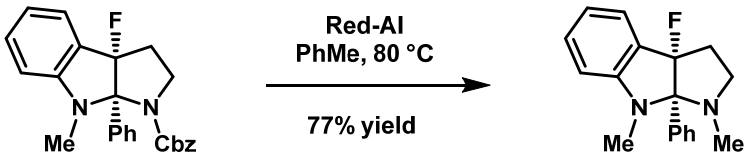
TLC R_f = 0.26 in 15% EtOAc/hexanes (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$, compound exists as a 1.1:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) δ 7.51 – 7.28 (m, 10H*, 10H§), 7.18 (dt, *J* = 14.7, 7.2 Hz, 1H*, 1H§), 6.86 – 6.73 (m, 2H*, 2H§), 6.61 (d, *J* = 8.0 Hz, 1H*), 6.53 (d, *J* = 8.0 Hz, 1H§), 5.14 (d, *J* = 12.5 Hz, 1H*), 5.11 – 4.99 (m, 1H*, 1H§), 4.89 (d, *J* = 12.3 Hz, 1H§), 4.22 – 4.07 (m, 1H§), 4.03 (t, *J* = 9.7 Hz, 1H*), 3.35 (dd, *J* = 11.5, 6.3 Hz, 1H*), 3.26 (td, *J* = 11.9, 11.4, 6.4 Hz, 1H§), 3.04 (s, 3H*), 2.75 (s, 3H§), 2.67 – 2.37 (m, 2H*, 2H§) ppm.

^{13}C NMR (101 MHz, $CDCl_3$; compound exists as a 1.1:1 mixture of rotamers) δ 155.1, 154.4, 152.4, 152.2, 136.7, 135.6, 135.4, 134.4, 132.2, 132.2, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 124.7, 124.6, 123.3, 123.1, 118.2, 117.9, 106.9, 92.9, 92.6, 77.5, 77.2, 76.8, 67.3, 67.0, 46.3, 46.2, 32.0, 31.5, 31.2, 30.9 ppm.

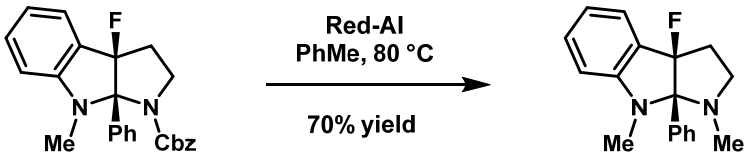
FTIR 3034, 2927, 2894, 1714, 1613, 1493, 1448, 1401, 1340, 1191, 1104, 1004, 960 (NaCl/thin film): cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{25}H_{24}FN_2O_2$ $[M+H]^+$: 403.1816, found: 403.1799.



(+)-8 (+)-9

A flame-dried 25 mL round-bottom flask was charged with (+)-**8** (12.5 mg, 31 μmol) and PhMe (620 μL). Red-Al (60 wt% in PhMe, 80 μL, 248 μmol, 8.0 equiv) was added dropwise. After stirring for 5 min, the flask was flushed with argon, sealed, and the reaction was stirred at 80 °C for 1.5 h. The solution was cooled to room temperature and then slowly quenched with a 1 M aqueous solution of Rochelle's salt (1 mL). The resulting mixture was stirred vigorously for 1 h and then extracted with Et_2O (3 mL x 4). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (2–7% EtOAc/hexanes) to afford (+)-**9** (6.8 mg, 77% yield) as a white crystalline solid.



(–)-8 (–)-9

The same procedure was performed on (–)-**8** (13 mg, 32 μmol) to afford (–)-**9** (6.4 mg, 70%

yield) as a white crystalline solid.

(+)-9:

$[\alpha]_D^{25}$ = +62.0° (c = 0.34, $CHCl_3$).

SFC: >99% ee (AD-H column: 12 min, 5% *i*-PrOH/CO_2; retention time = 5.3 min).

(–)-9:

$[\alpha]_D^{25}$ = –78.9° (c = 0.32, $CHCl_3$).

SFC: 99% ee (AD-H column: 12 min, 5% *i*-PrOH/CO_2; retention time = 10.8 min).

TLC R_f = 0.57 in 5% EtOAc/hexanes (UV, $KMnO_4$).

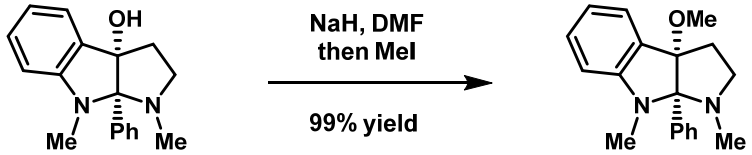
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 5H), 7.28 (d, *J* = 1.7 Hz, 1H), 7.26 (d, *J* = 1.5 Hz, 1H), 6.73 (tt, *J* = 7.4, 0.8 Hz, 1H), 6.47 (dq, *J* = 7.6, 1.1 Hz, 1H), 3.15 – 2.99 (m, 1H), 2.73 (d, *J* = 0.9 Hz, 3H), 2.64 – 2.40 (m, 2H), 2.47 (s, 3H), 2.39 – 2.28 (m, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5 (d, *J* = 5.2 Hz), 136.3 (d, *J* = 6.3 Hz), 131.1 (d, *J* = 2.7 Hz), 128.7 (d, *J* = 1.5 Hz), 128.3, 128.1, 126.1 (d, *J* = 24.0 Hz), 124.8, 117.2 (d, *J* = 2.6 Hz), 109.6, 107.6, 104.8, 96.5 (d, *J* = 19.9 Hz), 51.4 (d, *J* = 6.2 Hz), 38.0 (d, *J* = 30.0 Hz), 36.4, 34.0 ppm.

^{19}F NMR (300 MHz, $CDCl_3$) δ –128.6 ppm.

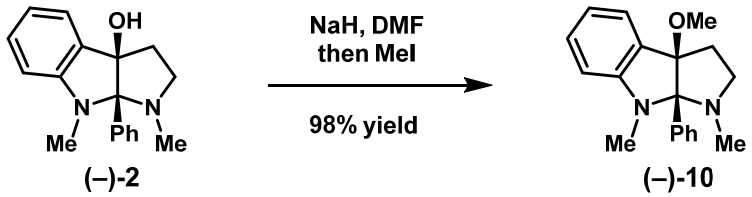
FTIR 2936, 2794, 1612, 1494, 1446, 1370, 1310, 1213, 1100, 1026, 940 (NaCl/thin film): cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{18}H_{20}FN_2$ $[M+H]^+$: 283.1605, found: 283.1603.



(+)-2 (+)-10

A flame-dried 15 mL round-bottom flask was charged with sodium hydride (60% dispersion in oil, 7 mg, 182 μmol, 3.0 equiv) and DMF (300 μL). The solution was cooled to 0 °C and a solution of (+)-**2** (17 mg, 61 μmol) in DMF (500 μL) was added dropwise. The ice bath was removed and the solution was allowed to warm to ambient temperature over 20 min. Methyl iodide (20 μL, 303 μmol, 5.0 equiv) was added dropwise. After stirring for 1.5 h, the reaction was quenched with a solution of H_2O and saturated aqueous NH_4Cl (3:1 v/v ratio, 2 mL). The resulting mixture was extracted with Et_2O (3 mL x 4) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (2–7% EtOAc/hexanes) to afford (+)-**10** (18 mg, >99% yield) as a yellow viscous oil.



The same procedure was performed on (–)-**2** (17 mg, 61 μmol) to afford (–)-**10** (17.5 mg, 98% yield) as a yellow viscous oil.

(+)-10:

$[\alpha]_D^{25}$ = +131.6° (c = 0.90, $CHCl_3$).

SFC: 97% ee (AD-H column: 12 min, 10% *i*-PrOH/CO_2; retention time = 4.5 min).

(–)-10:

$[\alpha]_D^{25}$ = –139.9° (c = 0.875, $CHCl_3$).

SFC: >99% ee (AD-H column: 12 min, 10% *i*-PrOH/CO_2; retention time = 3.5 min).

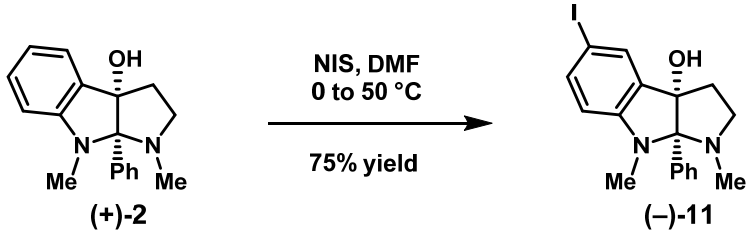
TLC R_f = 0.63 in 17% EtOAc/hexanes (UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (br s, 2H), 7.38 – 7.32 (m, 2H), 7.33 – 7.26 (m, 1H), 7.23 (ddd, *J* = 7.8, 7.4, 1.3 Hz, 1H), 7.12 (ddd, *J* = 7.3, 1.4, 0.5 Hz, 1H), 6.69 (td, *J* = 7.3, 1.0 Hz, 1H), 6.44 (d, *J* = 7.8 Hz, 1H), 3.08 – 2.98 (m, 1H), 2.82 (s, 3H), 2.64 (s, 3H), 2.55 (ddd, *J* = 11.8, 8.6, 4.7 Hz, 1H), 2.51 – 2.42 (m, 1H), 2.42 (s, 3H), 2.16 – 2.07 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 137.8, 129.9, 129.6, 127.9, 127.7, 127.5, 124.8, 116.4, 104.1, 96.3, 96.2, 52.4, 51.5, 37.6, 36.5, 33.8 ppm.

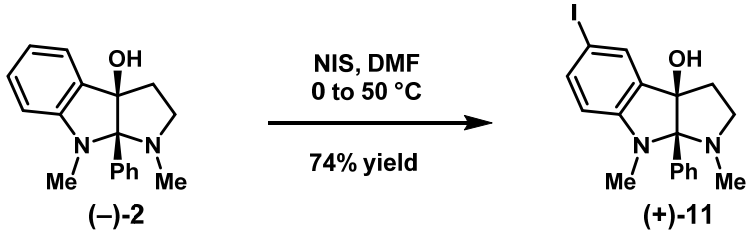
FTIR (NaCl/thin film): 3386, 3053, 2934, 2792, 1607, 1495, 1446, 1373, 1310, 1261, 1217, 1161, 1119, 1039, 972 cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{19}H_{23}N_2O$ $[M+H]^+$: 295.1805, found: 295.1811.



A flame-dried 25 mL round-bottom flask was charged with (+)-**2** (37 mg, 132 μmol) and DMF (1.6 mL). The solution was cooled to 0 °C and a solution of *N*-iodosuccinimide (39 mg, 172 μmol, 1.3 equiv) in DMF (1 mL) was added dropwise over 2 min. After stirring for 10 min, the reaction was allowed to warm to room temperature over 20 min, and then warmed to 50 °C and stirred for 3 h. After this time, the reaction was cooled to room

temperature and quenched with a 2:1 solution of H_2O and 10 wt% $Na_2S_2O_3$ (aq) (5 mL). The resulting mixture was extracted with Et_2O (3 mL x 4). The combined organic extracts were washed with brine (1.5 mL x 1) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (5–15% EtOAc/hexanes) to afford (–)-**11** (40 mg, 75% yield) as a viscous yellow oil.



(–)-2 (+)-11

The same procedure was performed on (–)-**2** (40 mg, 143 μmol) to afford (+)-**11** (42.7 mg, 74% yield) as a viscous yellow oil.

(–)-11:

$[\alpha]_D^{25}$ = –7.2° (c = 1.00, $CHCl_3$).

SFC: 96.4% ee (AD-H column: 12 min, 25% *i*-PrOH/CO_2; retention time = 8.6 min).

(+)-11:

$[\alpha]_D^{25}$ = +6.3° (c = 1.00, $CHCl_3$).

SFC: >99% ee (AD-H column: 12 min, 25% *i*-PrOH/CO_2; retention time = 6.7 min).

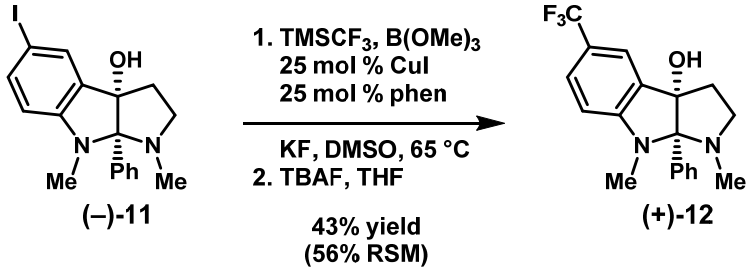
TLC R_f = 0.42 in 15% EtOAc/hexanes (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.43 (m, 2H), 7.43 – 7.35 (m, 2H), 7.32 (tt, *J* = 7.1, 1.5 Hz, 1H), 6.23 (d, *J* = 9 Hz, 1H), 3.04 (ddd, *J* = 9.2, 5.3, 2.4 Hz, 1H), 2.73 (s, 3H), 2.68 – 2.51 (m, 1H), 2.47 (s, 3H), 2.28 – 2.16 (m, 2H), 1.37 (br s, 1H) ppm. Note: A total of 6H aromatic protons observed with relaxation delay = 1 sec; 8H expected if relaxation delay is > 5 sec.

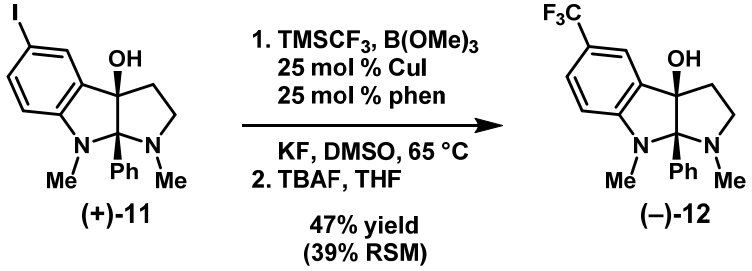
^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 138.5, 136.8, 133.7, 132.7, 129.1, 128.4, 106.6, 98.7, 90.3, 51.5, 40.7, 36.7, 34.5 ppm.

FTIR 3540, 3448, 3059, 2935, 2794, 1596, 1487, 1446, 1367, 1267, 1164, 1106, 1028, 986 (NaCl/thin film): cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{18}H_{20}IN_2O$ $[M+H]^+$: 407.0615, found: 407.0603.



A 1 dram vial containing (–)-**11** (30 mg, 74 μmol) and 1,10-phenanthroline (3.5 mg, 20 μmol, 0.25 equiv) was transferred to a nitrogen filled glovebox and charged with KF (14 mg, 236 μmol, 3.0 equiv), CuI (3.8 mg, 20 μmol, 0.25 equiv), and DMSO (390 μL). The vial was removed from the glovebox and trimethyl borate (26 μL, 236 μmol, 3.0 equiv) and $TMSCF_3$ (35 μL, 236 μmol, 3.0 equiv) were added. The vial was flushed with argon and sealed with a Teflon cap and then stirred at 65 °C for 24 h. The reaction mixture was then cooled to room temperature and water (0.5 mL) was added. The solution was filtered through a small pad of Celite and rinsed copiously with Et_2O (5 mL). The solution was washed with water (2.5 mL) and the aqueous layer was extracted with Et_2O (4 mL x 3). The combined organic solutions were washed with brine (2 mL x 1), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was dissolved in THF (790 μL) and TBAF (1.0 M in THF, 20 μL, 197 μmol, 2.5 equiv) was added dropwise. The solution was stirred for 1.5 h and then quenched with brine (2 mL). The mixture was stirred vigorously for 20 min and then extracted with Et_2O (4 mL x 3). The combined organic solutions were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel chromatography (0–2% EtOAc/CH_2Cl_2) to afford (+)-**12** (11.0 mg, 43% yield) as a yellow solid and recovered (–)-**11** (16.5 mg, 56% yield RSM) as a yellow solid.



The same procedure was performed on (+)-**11** (32 mg, 79 μmol) to afford (–)-**12** (13.0 mg, 47% yield) as a yellow solid and recovered (+)-**11** (12.5 mg, 39% yield RSM) as a yellow solid.

(+)-12:

$[\alpha]_D^{25}$ = +7.5° (c = 0.65, $CHCl_3$).

SFC: 98% ee (AD-H column: 12 min, 10% *i*-PrOH/CO_2; retention time = 9.5 min).

(–)-12:

$[\alpha]_D^{25}$ = –13.1° (c = 0.62, $CHCl_3$).

SFC: >99% ee (AD-H column: 12 min, 10% *i*-PrOH/CO_2; retention time = 6.5 min).

TLC R_f = 0.28 in 10% EtOAc/hexanes (UV, $KMnO_4$).

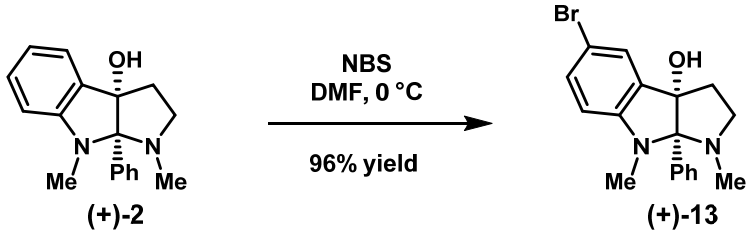
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 2H), 7.44 – 7.30 (m, 3H), 6.43 (d, *J* = 8.3 Hz, 1H), 3.14 – 2.99 (m, 1H), 2.80 (s, 3H), 2.62 – 2.53 (m, 1H), 2.50 (s, 3H), 2.26 (dd, *J* = 7.8, 3.1 Hz, 2H), 1.40 (br s, 1H) ppm. Note: A total of 6H aromatic protons observed with relaxation delay = 1 sec; 8H expected if relaxation delay is > 5 sec.

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.82, 136.58, 131.09, 129.14, 128.58, 127.94 (q, *J* = 3.8 Hz), 126.59, 123.91, 121.51 (q, *J* = 3.6 Hz), 103.51, 99.04, 90.15, 51.46, 40.71, 36.66, 34.38 ppm.

^{19}F NMR (300 MHz, $CDCl_3$) δ –60.4 ppm.

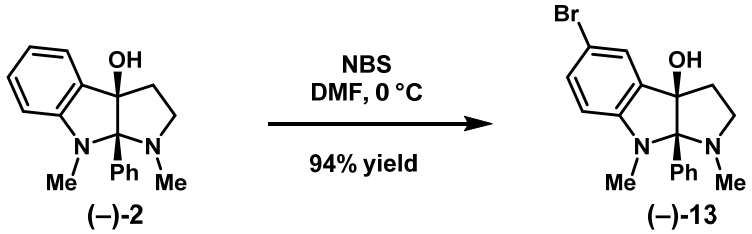
FTIR 3436, 3058, 2934, 2797, 1703, 1622, 1516, 1446, 1383, 1326, 1271, 1108 (NaCl/thin film): cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{19}H_{20}F_3N_2O$ $[M+H]^+$: 349.1522, found: 349.1504.



(+)-2 (+)-13

A flame-dried 25 mL round-bottom flask was charged with (+)-**2** (63 mg, 225 μmol) and DMF (4 mL). The solution was cooled to 0 °C and a solution of *N*-bromosuccinimide (40 mg, 222 μmol, 0.99 equiv) in DMF (1 mL) was added dropwise over 10 min. After stirring for 0.5 h, a solution of H_2O and 10 wt% $Na_2S_2O_3$ (aq) (6:1 v/v ratio, 6 mL) was added. The resulting mixture was extracted with Et_2O (2 mL x 4) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (5–15% EtOAc/hexanes) to afford (+)-**13** (77 mg, 96% yield) as a light-yellow foam.



The same procedure was performed on (–)-**2** (63 mg, 225 μmol) to afford (–)-**13** (75.5 mg, 94% yield) as a white foam.

(+)-13:

[α]$_D^{25}$ = +3.9° (c = 1.00, $CHCl_3$).

SFC: 98% ee (AD-H column: 12 min, 20% *i*-PrOH/CO_2; retention time = 8.6 min).

(–)-13:

[α]$_D^{25}$ = –4.4° (c = 1.00, $CHCl_3$).

SFC: >99% ee (AD-H column: 12 min, 20% *i*-PrOH/CO_2; retention time = 9.6 min).

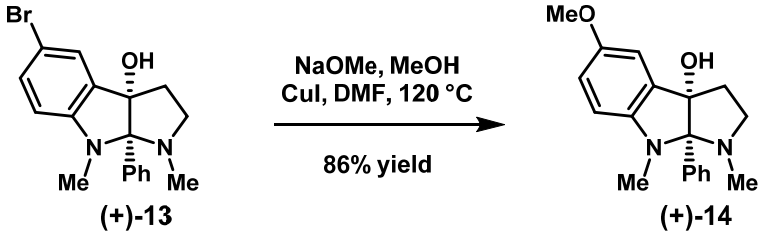
TLC R_f = 0.26 in 10% EtOAc/hexanes (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (br t, *J* = 7.4 Hz, 2H), 7.36 – 7.27 (m, 3H), 6.30 (d, *J* = 8.2 Hz, 1H), 3.14 – 2.98 (m, 1H), 2.73 (s, 3H), 2.66 – 2.51 (m, 1H), 2.47 (s, 3H), 2.30 – 2.18 (m, 2H), 1.38 (br s, 1 H) ppm. Note: A total of 6H aromatic protons observed with relaxation delay = 1 sec; 8H expected if relaxation delay is > 5 sec.

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6, 136.8, 133.1, 132.6, 129.0, 128.4, 127.1, 108.2, 105.7, 98.9, 90.3, 51.5, 40.7, 36.7, 34.6 ppm.

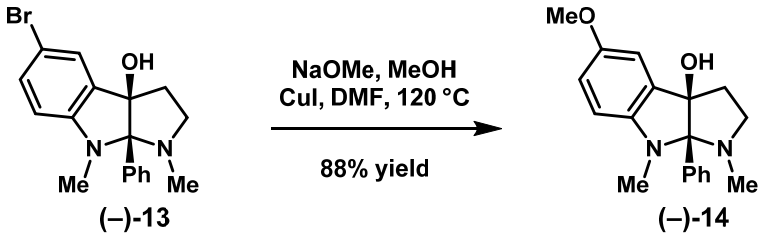
FTIR 3544, 3445, 3057, 2937, 2794, 1601, 1491, 1445, 1368, 1265, 1162, 1106, 1028, 987, 938 (NaCl/thin film): cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{18}H_{20}BrN_2O$ $[M+H]^+$: 359.0754, found: 359.9767.



A 2 dram vial containing (+)-**13** (20 mg, 56 μmol) was charged with CuI (21 mg, 835 μmol, 2.0 equiv) in a nitrogen-filled glovebox. The vial was removed from the glovebox and dry DMF (560 μL) was added followed by a freshly prepared solution of NaOMe in MeOH (4.0 M, 210 μL, 15.0 equiv) prepared by slowly adding Na portion wise to dry MeOH and stirring overnight. The vial was sealed under argon with a Teflon cap and stirred at 120 °C for 2 h.

The reaction mixture was then cooled to room temperature and filtered through a pad of Celite and rinsed copiously with Et_2O (12 mL). The organic filtrate was washed with water (3 mL x 1) and the aqueous layer was extracted with Et_2O (2 mL x 3). The combined organic solutions were washed with brine (2 mL x 1), and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10–25% EtOAc/hexanes) to afford (+)-**14** (15 mg, 86% yield) as a light yellow oil.



(–)-13 (–)-14

The same procedure was performed on (–)-**13** (20 mg, 56 μmol) to afford (–)-**14** (15.3 mg, 88% yield) as a light yellow oil.

(+)-14:

$[\alpha]_D^{25}$ = +1.9° (c = 0.75, $CHCl_3$).

SFC: 97% ee (AD-H column: 12 min, 20% *i*-PrOH/CO_2; retention time = 8.2 min).

(–)-14:

$[\alpha]_D^{25}$ = –4.0° (c = 0.77, $CHCl_3$).

SFC: >99% ee (AD-H column: 12 min, 20% *i*-PrOH/CO_2; retention time = 7.5 min).

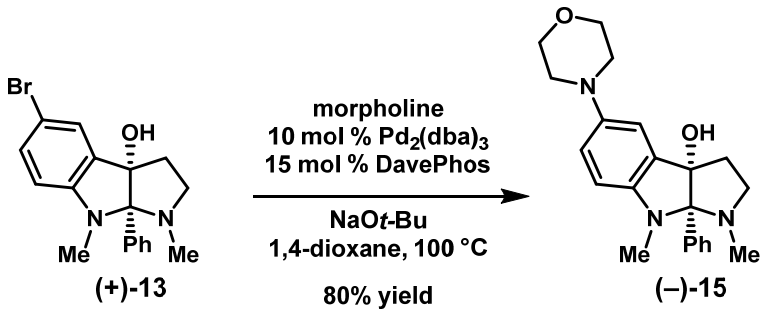
TLC R_f = 0.19 in 20% EtOAc/hexanes (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (br t, *J* = 7.4 Hz, 2H), 7.31 (ddd, *J* = 8.5, 7.0, 1.6 Hz, 1H), 6.90 (d, *J* = 2.6 Hz, 1H), 6.81 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.34 (d, *J* = 8.5 Hz, 1H), 3.76 (s, 3H), 3.12 – 2.97 (m, 1H), 2.72 (s, 3H), 2.66 – 2.53 (m, 1H), 2.47 (s, 3H), 2.30 – 2.20 (m, 2H), 1.38 (br s, 1H) ppm. Note: A total of 6H aromatic protons observed with relaxation delay = 1 sec; 8H expected if relaxation delay is > 5 sec.

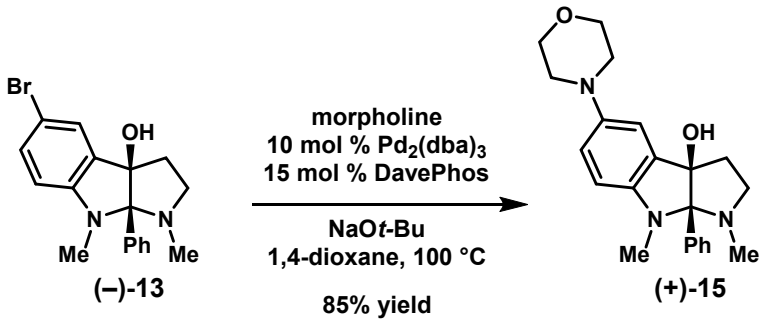
^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 147.3, 137.5, 131.9, 128.9, 128.1, 115.5, 110.6, 104.4, 98.9, 90.9, 56.3, 51.7, 40.8, 36.7, 35.1 ppm.

FTIR 3470, 2936, 2816, 1622, 1598, 1504, 1446, 1361, 1274, 1216, 1114, 1027, 988 (NaCl/thin film): cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{19}H_{23}N_2O_2$ $[M+H]^+$: 311.1754, found: 311.1744.



A 2 dram vial containing (+)-**13** (15 mg, 42 μmol) was charged with DavePhos (2.5 mg, 6 μmol, 0.15 equiv) in a nitrogen-filled glovebox. The vial was removed from the glovebox and 1,4-dioxane (300 μL), $Pd_2(dba)_3$ (3.8 mg, 4 μmol, 0.10 equiv), NaO*t*-Bu (8 mg, 84 μmol, 2.0 equiv), and morpholine (10 μL, 13 μmol, 3.0 equiv) were added. The vial was sealed under argon with a Teflon cap and stirred at 100 °C for 4 h. The reaction mixture was then cooled to room temperature and diluted with CH_2Cl_2 (2 mL). The solution was washed with water (2 mL x 1) and the aqueous layer was extracted with CH_2Cl_2 (2 mL x 3). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (25–60% EtOAc/CH_2Cl_2), and the isolated fractions purified again by silica gel chromatography (33–75% EtOAc/hexanes), to give (–)-**15** (12.3 mg, 80% yield) as a yellow oil.



The same procedure was performed on (–)-**13** (20 mg, 56 μmol) to afford (+)-**15** (13.0 mg, 85% yield) as a yellow oil.

(–)-15:

$[\alpha]_D^{25}$ = –13.1° (c = 0.62, $CHCl_3$).

SFC: 98% ee (AD-H column: 12 min, 25% *i*-PrOH/CO_2; retention time = 8.0 min).

(+)-15:

$[\alpha]_D^{25}$ = +7.5° (c = 0.65, $CHCl_3$).

SFC: >99% ee (AD-H column: 12 min, 25% *i*-PrOH/CO_2; retention time = 6.5 min).

TLC R_f = 0.32 in 60% EtOAc/hexanes (UV, $KMnO_4$).

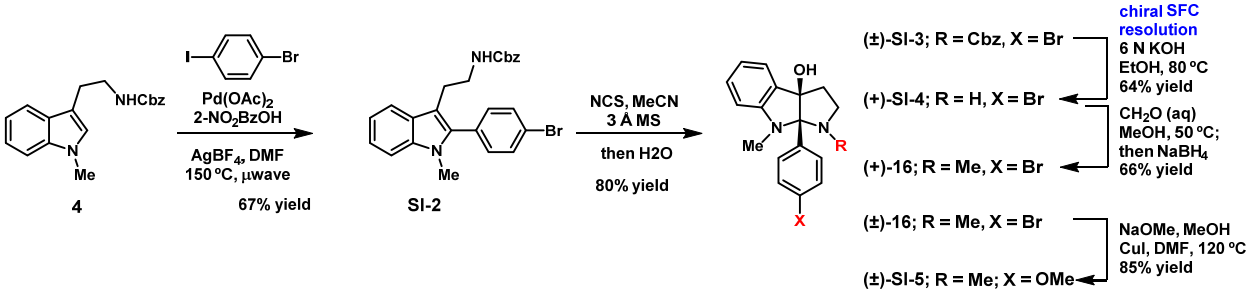
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.27 (m, 4H), 6.98 (br d, *J* = 2.5 Hz, 1H), 6.85 (br d, *J* = 8.4 Hz, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 3.85 (t, *J* = 4.7 Hz, 4H), 3.04 (d, *J* = 4.6 Hz, 5H), 2.72 (s, 3H), 2.65 – 2.52 (m, 1H), 2.46 (s, 3H), 2.34 – 2.15 (m, 2H), 1.37 (br s, 1H) ppm. Note: A total of 7H aromatic protons observed with relaxation delay = 1 sec; 8H expected if relaxation delay is > 5 sec.

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8, 143.7, 137.5, 131.9, 128.9, 128.2, 118.7, 114.5, 104.4, 98.9, 91.0, 67.3, 51.8, 51.6, 40.7, 36.7, 34.9 ppm.

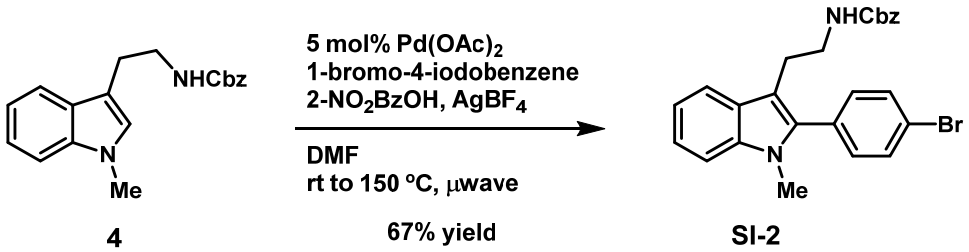
FTIR 3407, 2933, 2856, 2815, 1622, 1503, 1446, 1360, 1296, 1257, 1215, 1118, 1028 (NaCl/thin film): cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{22}H_{28}N_3O_2$ $[M+H]^+$: 366.2176, found: 366.2181.

Scheme S1. Synthesis of Aryl Bromide 16.



Synthesis of Aryl Bromide 16



On a benchtop, a 10–20 mL microwave vial was charged with **4** (600 mg, 1.95 mmol), DMF (7.8 mL), 2-nitrobenzoic acid (488 mg, 2.92 mmol, 1.5 equiv), 1-bromo-4-iodobenzene (2.20 g, 7.78 mmol, 4.0 equiv), $Pd(OAc)_2$ (22 mg, 97 μmol, 0.05 equiv), and then $AgBF_4$ (568 mg, 2.92 mmol, 1.5 equiv). A magnetic vane stirbar was added and the reaction was flushed with argon and capped using a microwave vial crimper. The solution was then stirred vigorously (660 rpm) in the dark for 40 min. The black-brown opaque solution was then subjected to microwave irradiation using a Biotage microwave reactor for 4 min at 150 °C (stirred at 660 rpm). The reaction was filtered over a short plug of Celite, eluting with

EtOAc (40 mL). The filtrate was washed with saturated aqueous NH_4Cl (15 mL x 2), saturated aqueous $NaHCO_3$ (15 mL x 2), and brine (15 mL x 2) and the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (5–25% EtOAc/hexanes) to afford **SI-2** (606 mg, 67% yield) as a yellow foam.

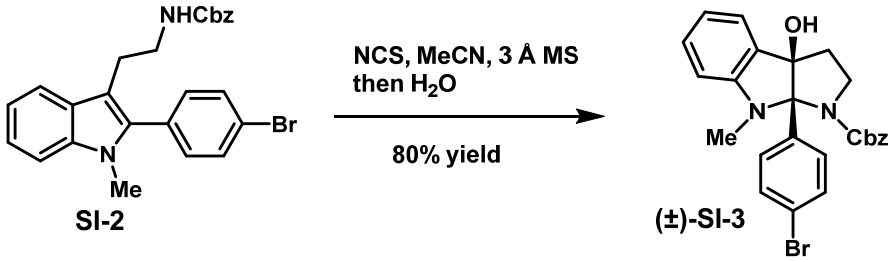
TLC R_f = 0.33 in 15% EtOAc/hexanes (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$, compound exists as a 6.6:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) 7.65 (d, *J* = 7.9 Hz, 1H*, 1H§), 7.61 – 7.54 (m, 3H*), 7.54 – 7.47 (m, 3H§), 7.41 – 7.27 (m, 6H*, 6H§), 7.25 – 7.20 (m, 2H*, 2H§), 7.16 (t, *J* = 7.6 Hz, 1H*), 7.15 – 7.07 (br s, 1H§), 5.04 (s, 2H*, 2H§), 4.71 (t, *J* = 6.2 Hz, 1H*), 4.50 (br s, 1H§), 3.56 (s, 3H*, 3H§), 3.42 (q, *J* = 6.7 Hz, 2H*), 3.41 – 3.31 (br s, 2H§), 2.91 (t, *J* = 6.9 Hz, 2H*, 2H§) ppm.

^{13}C NMR (101 MHz, $CDCl_3$; compound exists as a 6.6:1 mixture of rotamers, only the major rotamer is reported) 156.3, 137.6, 137.4, 136.8, 132.3, 131.9, 130.7, 128.6, 128.2, 128.2, 127.5, 122.8, 122.3, 119.8, 119.1, 110.2, 109.6, 66.6, 41.8, 31.0, 25.3 ppm.

FTIR (NaCl/thin film): 3426, 3342, 3052, 2940, 1714, 1514, 1470, 1360, 1234, 1133, 1072, 1009, 908 cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{25}H_{24}BrN_2O_2$ $[M+H]^+$ 463.1016, found: 463.0994.



A flame-dried 250 mL round-bottom flask was charged with **SI-2** (495 mg, 1.07 mmol), MeCN (11 mL), and activated 3Å molecular sieve pellets (673 mg, 1.3 x mass of **SI-2**). A solution of *N*-chlorosuccinimide (179 mg, 1.34 mmol, 1.26 equiv) in MeCN (22 mL) was added dropwise over 5 min. The flask was wrapped in aluminum foil and stirred in the dark for 3 h. TLC analysis indicated consumption of starting material (R_f of the putative chloride intermediate = 0.61; 33% EtOAc/hexanes, UV, $KMnO_4$). Water (22 mL) was then added dropwise and the reaction was stirred for 1 h. The reaction mixture was filtered through a Celite pad and rinsed copiously with EtOAc (30 mL). A 2:1 mixture of saturated aqueous $NaHCO_3$/brine (20 mL) was added and the layers were partitioned in a separatory funnel. The aqueous layer was extracted with EtOAc (30 mL x 3) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The

crude residue was purified by silica gel chromatography (10–25% EtOAc/hexanes) to afford (±)-**SI-3** (410 mg, 80% yield) as a yellow foam.

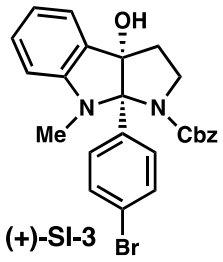
TLC R_f = 0.49 in 33% EtOAc/hexanes (UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$, compound exists as a 1.2:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) 7.56 – 7.05 (m, 10H*, 10H§), 6.87 – 6.73 (m, 2H*, 2H§), 6.57 (d, *J* = 7.9 Hz, 1H*), 6.51 (d, *J* = 8.1 Hz, 1H§), 5.22 – 4.97 (m, 2H*, 1H§), 4.81 (d, *J* = 12.2 Hz, 1H§), 4.08 – 3.87 (m, 1H*, 1H§), 3.26 (td, *J* = 11.2, 6.1 Hz, 1H*), 3.17 (td, *J* = 11.7, 5.8 Hz, 1H§), 3.00 (s, 3H*), 2.75 (s, 3H§), 2.53 – 2.35 (m, 2H*), 2.21 (dddd, *J* = 13.6, 10.1, 6.6, 2.9 Hz, 2H§), 1.51 (br s, 1H*, 1H§) ppm.

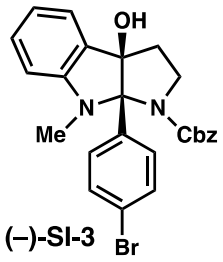
^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 1.2:1 mixture of rotamers) 154.9, 154.6, 151.1, 150.9, 136.7, 136.3, 135.5, 135.3, 133.4, 131.9, 131.8, 131.1, 129.3, 128.6, 128.4, 128.2, 128.1, 128.1, 128.0, 127.9, 123.8, 122.7, 122.4, 118.6, 118.2, 106.9, 106.8, 93.9, 93.2, 90.0, 88.9, 67.3, 67.0, 46.4, 46.3, 34.3, 33.8, 31.9, 31.3 ppm.

FTIR (NaCl/thin film): 3405, 3053, 3032, 2890, 1694, 1609, 1488, 1394, 1348, 1185, 1119, 1001 cm^{-1}.

HRMS (TOF-ESI, *m/z*) calc'd for $C_{25}H_{24}BrN_2O_3$ $[M+H]^+$ 479.0965, found 479.0979.



(+)-SI-3



(–)-SI-3

Preparative chiral SFC resolution: Carbamate (±)-**SI-3** (240 mg) was dissolved in a minimal amount of IPA (~4 mL). This solution of racemic compound was resolved by preparative chiral SFC using serial injections (isocratic: 45% *i*-PrOH/CO_2) to afford (–)-**SI-3** (118 mg) and (+)-**SI-3** (107 mg) as yellow foams.

(+)-SI-3:

$[\alpha]_D^{25}$ = +269.1° (c =1.00, $CHCl_3$).

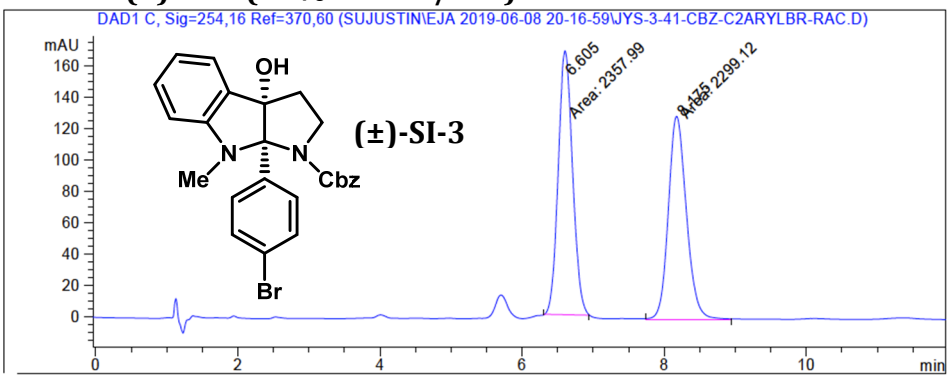
SFC: 97% ee (AD-H column: 12 min, 35% *i*-PrOH/CO_2; retention time = 8.4 min).

(–)-SI-3:

$[\alpha]_D^{25}$ = –253.8° (c = 1.00, $CHCl_3$).

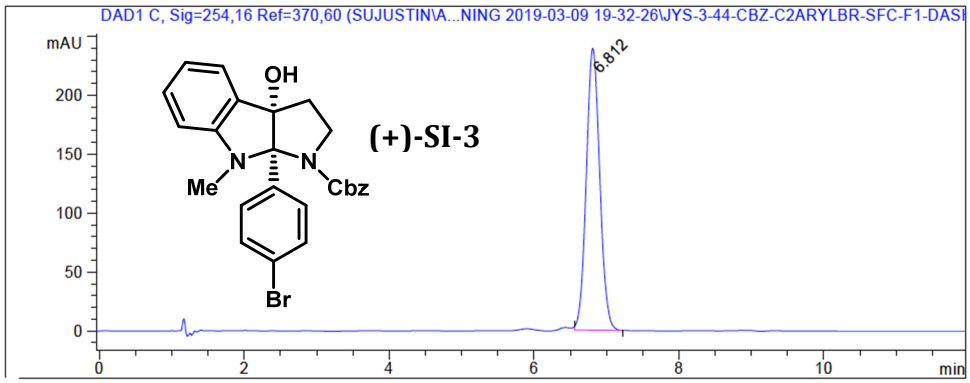
SFC: >99% ee (AD-H column: 12 min, 35% *i*-PrOH/CO_2; retention time = 6.8 min).

Chiral SFC trace of (±)-SI-3 (35% *i*-PrOH/CO_2):



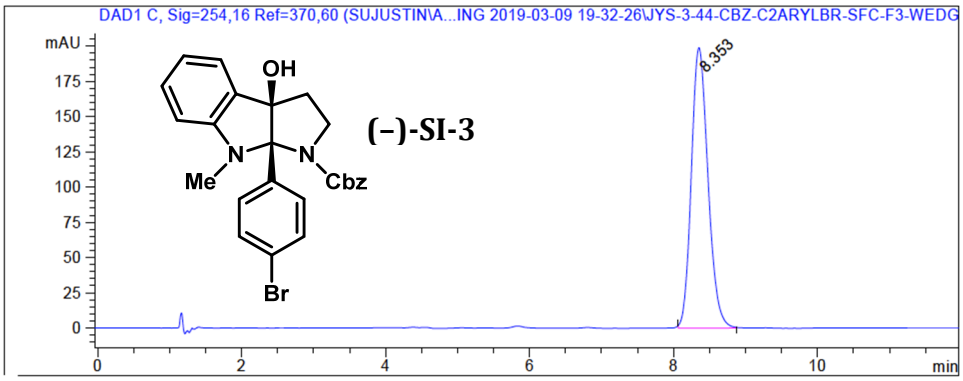
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.605	MM	0.2336	2357.98682	168.25053	50.6320
2	8.175	MM	0.2955	2299.11670	129.66197	49.3680

Chiral SFC trace of (+)-SI-3 (35% *i*-PrOH/CO_2):

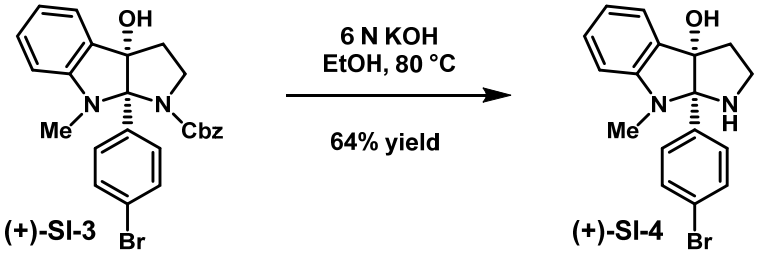


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.812	BB	0.2027	3086.10864	238.96965	100.0000

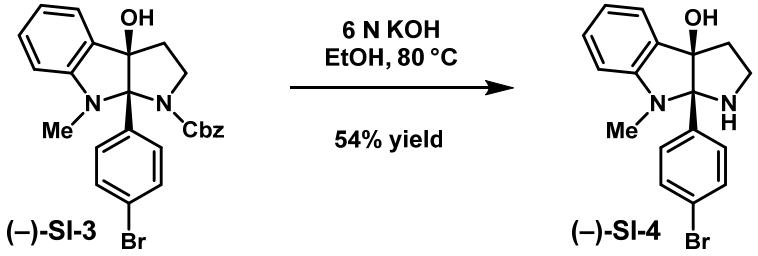
Chiral SFC trace of (–)-SI-3 (35% *i*-PrOH/CO_2):



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.353	BB	0.2478	3199.50537	198.78656	100.0000



A 25 mL round-bottom flask containing (+)-**SI-3** (31 mg, 65 μmol) was charged with EtOH (0.8 mL) and 6 N aqueous solution of potassium hydroxide (540 μL). The flask was sealed under argon and heated to 80 °C. After stirring for 76 h, the red solution was cooled to room temperature. The crude mixture was filtered through Celite and rinsed with EtOAc (5 mL). The combined organic filtrates were washed with water (2 mL) and the aqueous layer was extracted with EtOAc (3 mL x 3). The combined organics were washed with brine (2 mL, x 1) and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10–33% EtOAc/hexanes) to afford (+)-**SI-4** (14 mg, 64% yield) as an amber yellow oil.



The same procedure was performed on (–)-**SI-3** (45 mg, 94 μmol) to afford (–)-**SI-4** (17.5 mg, 54% yield) as a pale-yellow oil.

(+)-SI-4:

$[\alpha]_D^{25}$ = +39.6° (c = 0.70, MeOH).

SFC: 95% ee (AD-H column: 12 min, 30% *i*-PrOH/CO_2; retention time = 8.3 min).

(–)-SI-4:

$[\alpha]_D^{25}$ = –43.3° (c = 0.875, MeOH).

SFC: >99% ee (AD-H column: 12 min, 30% *i*-PrOH/CO_2; retention time = 5.7 min).

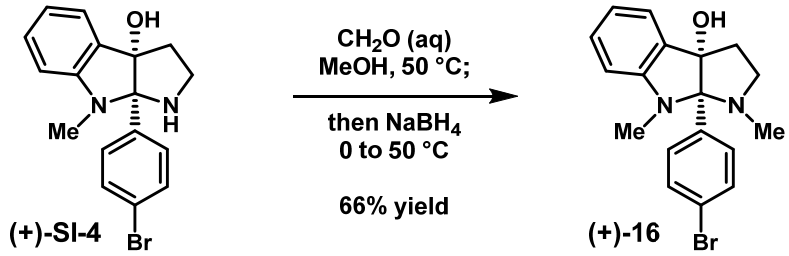
TLC R_f = 0.28 in 30% EtOAc/hexanes (UV, $KMnO_4$).

^{1}H NMR (400 MHz, CD_3CN) δ 7.49 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.19 – 7.11 (m, 2H), 6.63 (td, *J* = 7.4, 1.0 Hz, 1H), 6.43 (dd, *J* = 8.4, 1.0 Hz, 1H), 3.11 (ddd, *J* = 9.3, 5.3, 3.2 Hz, 1H), 2.80 (br s, 1H), 2.70 – 2.62 (m, 1H), 2.57 (s, 3H), 2.20 – 2.10 (m, 2H) ppm. Note: One of the *N*–H/*O*–H protons was not observed under these conditions.

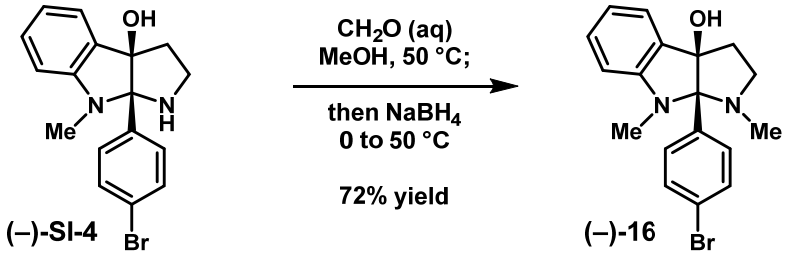
^{13}C NMR (101 MHz, CD_3CN) δ 152.5, 140.7, 132.1, 131.7, 131.3, 130.6, 124.7, 121.8, 117.6, 105.3, 94.5, 90.4, 43.8, 42.6, 28.6 ppm.

FTIR 3363, 3053, 2932, 2856, 1608, 1494, 1374, 1306, 1205, 1120, 1071 (NaCl/thin film): cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{17}H_{18}BrN_2O$ $[M+H]^+$: 345.0597, found: 345.0613.



A 1 dram vial containing (+)-**SI-4** (14 mg, 41 μmol) was charged with MeOH (340 μL) and CH_2O (37 wt% in H_2O, 45 μL). The vial was sealed, wrapped with aluminum foil, and stirred at 50 °C for 3 h. The solution was cooled to 0 °C and $NaBH_4$ (9 mg, 243 μmol, 6.0 equiv) was added. The reaction was allowed to warm to ambient temperature over 10 min and then covered with aluminum foil and heated at 50 °C. After stirring for 5 h, the reaction was cooled to room temperature and quenched with H_2O (2 mL). The mixture was extracted with EtOAc (3 mL x 4). The combined organic extracts were washed with brine (2 mL x 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (5–40% EtOAc/hexanes) to afford (+)-**16** (9.5 mg, 66% yield) as a yellow oil.



The same procedure was performed on (–)-**SI-4** (17 mg, 49 μmol) to afford (–)-**16** (12.7 mg, 72% yield) as a pale-yellow oil.

(+)-16:

$[\alpha]_D^{25}$ = +6.5° (c = 0.475, $CHCl_3$).

SFC: 96% ee (AD-H column: 12 min, 25% *i*-PrOH/CO_2; retention time = 7.6 min).

(–)-16:

$[\alpha]_D^{25}$ = –4.3° (c = 0.635, $CHCl_3$).

SFC: >99% ee (AD-H column: 12 min, 25% *i*-PrOH/CO_2; retention time = 6.3 min).

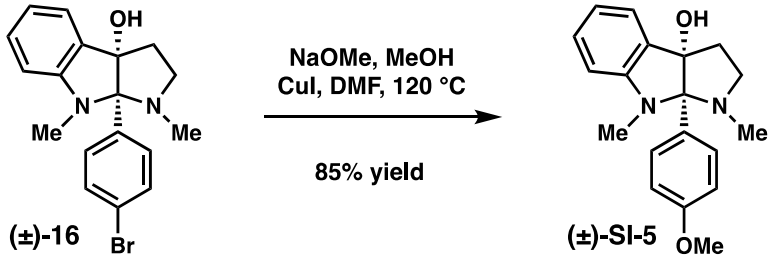
TLC R_f = 0.25 in 10% EtOAc/hexanes (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.22 (td, *J* = 7.0, 1.5 Hz, 2H), 6.71 (t, *J* = 7.4 Hz, 1H), 6.42 (d, *J* = 8.0 Hz, 1H), 3.01 (br s, 1H), 2.75 (s, 3H), 2.61 – 2.50 (m, 1H), 2.44 (s, 3H), 2.32 – 2.19 (m, 2H), 1.37 (br s, 1H) ppm. Note: A total of 6H aromatic protons observed with relaxation delay = 1 sec; 8H expected if relaxation delay is > 5 sec.

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4, 136.9, 132.0, 130.4, 130.2, 124.1, 122.3, 117.2, 104.3, 97.8, 90.9, 51.6, 40.5, 36.6, 34.3 ppm.

FTIR 3438, 3053, 2932, 2793, 1608, 1494, 1372, 1308, 1214, 1106, 1031 (NaCl/thin film): cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{18}H_{20}BrN_2O$ $[M+H]^+$: 359.0754, found: 359.0771.



A 2 dram vial containing (±)-**16** (8 mg, 22 μmol) was charged with CuI (8.5 mg, 45 μmol, 2.0 equiv) in a nitrogen-filled glovebox. The vial was removed from the glovebox and dry DMF (400 μL) and a freshly prepared solution of NaOMe in MeOH (4.0 M, 84 μL, 15.0 equiv) were added. The vial was flushed with argon and sealed with a Teflon cap and then stirred at 120 °C for 1.5 h. The reaction mixture was then cooled to room temperature and filtered through a pad of Celite and rinsed copiously with Et_2O (5 mL). The organic filtrate was washed with water (2 mL x 1) and the aqueous layer was extracted with Et_2O (3 mL x 3). The combined organic solutions were washed with brine (2 mL x 1), and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10–25% EtOAc/hexanes) to afford (±)-**SI-5** (5.9 mg, 85% yield) as a yellow oil.

TLC R_f = 0.38 in 25% EtOAc/hexanes (UV, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.16 (m, 2H), 6.91 (d, *J* = 7.9 Hz, 2H), 6.69 (td, *J* = 7.4, 1.0 Hz, 1H), 6.41 (d, *J* = 7.9 Hz, 1H), 3.81 (s, 3H), 3.01 (ddd, *J* = 8.3, 5.2, 2.3 Hz, 1H), 2.75 (s, 3H), 2.61 – 2.51 (m, 1H), 2.46 (s, 3H), 2.29 – 2.20 (m, 2H), 1.37 (br s, 1H) ppm. Note: A total of 6H aromatic protons observed with relaxation delay = 1 sec; 8H expected if relaxation delay is > 5 sec.

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 152.6, 130.9, 130.0, 129.2, 124.1, 116.9, 114.3, 104.1, 98.3, 90.4, 55.4, 51.6, 40.6, 36.7, 34.4 ppm.

FTIR (NaCl/thin film): 3478, 3051, 2934, 2791, 1608, 1494, 1372, 1304, 1245, 1172, 1106, 1031 cm^{-1}.

HRMS (TOF-ESI, *m/z*): calc'd for $C_{19}H_{23}N_2O_2$ $[M+H]^+$: 311.1754, found: 311.1743.

5. Absolute Stereochemical Assignment of (+)-2, (+)-6, and (+)-SI-3

Low-temperature diffraction data (φ- and ω-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON II CPAD detector with Cu-K_α radiation (λ = 1.54178 Å) from a $I_\mu S$ HB micro-focus sealed X-ray tube. All diffractometer manipulations, including data collection, integration, and scaling were carried out using the Bruker APEXII software.[7] Absorption corrections were applied using SADABS.[8] The structure was solved by intrinsic phasing using SHELXT[9] and refined against F^2 on all data by full-matrix least squares with SHELXL-2014[9] using established refinement techniques.[10] All non-hydrogen atoms were refined anisotropically. Unless otherwise noted, all hydrogen atoms were included into the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the *U* value of the atoms they are linked to (1.5 times for methyl groups and hydroxyl groups). Absolute configuration was determined by anomalous dispersion.[11] Graphical representation of the structures with 50% probability thermal ellipsoids was generated using Mercury visualization software.

Single crystal X-ray diffraction data for (+)-2

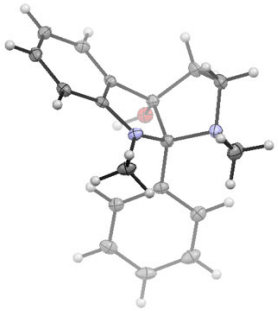


Figure S3: Structure of (+)-**2** with 50% probability anisotropic displacement ellipsoids.

Special Refinement Details for (+)-2

Compound (+)-**2** crystallizes in the monoclinic space group $P12_11$ with one molecule in the asymmetric unit. The coordinates for the hydrogen atom bound to O1 was located in the difference Fourier synthesis and refined using a riding model. No hydrogen bond acceptor was found for O1. Absolute configuration was determined by anomalous dispersion (Flack = -0.01(5)).[11]

Table S1. Crystal data and structure refinement for (+)-**2**.

Identification code	V18441
Empirical formula	$C_{18}H_{20}N_2O$
Formula weight	280.36
Temperature	99.99 K
Wavelength	1.54178 Å
Crystal system	Monoclinic

Space group	P 1 21 1	
Unit cell dimensions	a = 7.7914(9) Å	α= 90°.
	b = 8.3695(10) Å	β= 96.991(3)°.
	c = 11.3709(13) Å	γ= 90°.
Volume	735.98(15) $Å^3$	
Z	2	
Density (calculated)	1.265 Mg/m^3	
Absorption coefficient	0.620 mm^{-1}	
F(000)	300	
Crystal size	0.30 x 0.22 x 0.16 mm^3	
Theta range for data collection	3.917 to 79.687°.	
Index ranges	-9<=h<=9, -10<=k<=10, -14<=l<=14	
Reflections collected	24278	
Independent reflections	3062 [R(int) = 0.0517]	
Completeness to theta = 67.679°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7543 and 0.6759	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3062 / 1 / 196	
Goodness-of-fit on F^2	1.044	
Final R indices [I>2sigma(I)]	R1 = 0.0296, wR2 = 0.0781	
R indices (all data)	R1 = 0.0298, wR2 = 0.0782	
Absolute structure parameter	-0.01(5)	
Extinction coefficient	0.0170(17)	
Largest diff. peak and hole	0.227 and -0.202 $e.Å^{-3}$	

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for v18441_a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4721(2)	2843(1)	1638(1)	19(1)
N(1)	2689(2)	5966(2)	3084(1)	16(1)
N(2)	3419(2)	3554(2)	4304(1)	20(1)
C(9)	3841(2)	6733(2)	2445(1)	14(1)
C(6)	6489(2)	7834(2)	1221(2)	20(1)

C(5)	6414(2)	6214(2)	1516(1)	18(1)
C(18)	833(2)	1899(2)	2804(2)	20(1)
C(15)	-585(2)	3188(2)	651(2)	21(1)
C(16)	-1266(2)	1789(2)	1061(2)	23(1)
C(4)	5094(2)	5680(2)	2120(1)	14(1)
C(14)	766(2)	3960(2)	1332(2)	18(1)
C(7)	5219(2)	8880(2)	1522(1)	19(1)
C(13)	1484(2)	3333(2)	2420(1)	16(1)
C(2)	2984(2)	4204(2)	3114(1)	16(1)
C(1)	1035(2)	6703(2)	3215(2)	22(1)
C(3)	4758(2)	4012(2)	2541(1)	15(1)
C(17)	-545(2)	1142(2)	2135(2)	24(1)
C(8)	3872(2)	8348(2)	2128(1)	17(1)
C(11)	5240(2)	3923(2)	4667(2)	23(1)
C(12)	6061(2)	3443(2)	3577(2)	22(1)
C(10)	2297(2)	4004(3)	5187(2)	27(1)

Table S3. Bond lengths [Å] and angles [°] for v18441_a.

O(1)-C(3)	1.417(2)
O(1)-H(1)	0.86(3)
N(1)-C(9)	1.380(2)
N(1)-C(2)	1.493(2)
N(1)-C(1)	1.453(2)
N(2)-C(2)	1.460(2)
N(2)-C(11)	1.461(2)
N(2)-C(10)	1.458(2)
C(9)-C(4)	1.398(2)
C(9)-C(8)	1.399(2)
C(6)-H(6)	0.9500
C(6)-C(5)	1.400(2)
C(6)-C(7)	1.395(3)
C(5)-H(5)	0.9500
C(5)-C(4)	1.379(2)
C(18)-H(18)	0.9500

C(18)-C(13)	1.394(2)
C(18)-C(17)	1.391(3)
C(15)-H(15)	0.9500
C(15)-C(16)	1.389(3)
C(15)-C(14)	1.388(2)
C(16)-H(16)	0.9500
C(16)-C(17)	1.390(3)
C(4)-C(3)	1.509(2)
C(14)-H(14)	0.9500
C(14)-C(13)	1.396(2)
C(7)-H(7)	0.9500
C(7)-C(8)	1.396(2)
C(13)-C(2)	1.515(2)
C(2)-C(3)	1.607(2)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(3)-C(12)	1.534(2)
C(17)-H(17)	0.9500
C(8)-H(8)	0.9500
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(11)-C(12)	1.516(2)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800

C(3)-O(1)-H(1)	109.6(19)
C(9)-N(1)-C(2)	111.35(13)
C(9)-N(1)-C(1)	119.91(14)
C(1)-N(1)-C(2)	123.54(14)
C(2)-N(2)-C(11)	106.90(13)
C(10)-N(2)-C(2)	116.78(14)
C(10)-N(2)-C(11)	113.20(14)

N(1)-C(9)-C(4)	111.45(15)
N(1)-C(9)-C(8)	128.15(15)
C(4)-C(9)-C(8)	120.39(15)
C(5)-C(6)-H(6)	120.1
C(7)-C(6)-H(6)	120.1
C(7)-C(6)-C(5)	119.85(16)
C(6)-C(5)-H(5)	120.4
C(4)-C(5)-C(6)	119.25(15)
C(4)-C(5)-H(5)	120.4
C(13)-C(18)-H(18)	119.8
C(17)-C(18)-H(18)	119.8
C(17)-C(18)-C(13)	120.46(17)
C(16)-C(15)-H(15)	120.0
C(14)-C(15)-H(15)	120.0
C(14)-C(15)-C(16)	120.00(16)
C(15)-C(16)-H(16)	120.2
C(15)-C(16)-C(17)	119.55(16)
C(17)-C(16)-H(16)	120.2
C(9)-C(4)-C(3)	110.22(14)
C(5)-C(4)-C(9)	120.98(15)
C(5)-C(4)-C(3)	128.80(15)
C(15)-C(14)-H(14)	119.5
C(15)-C(14)-C(13)	120.92(16)
C(13)-C(14)-H(14)	119.5
C(6)-C(7)-H(7)	119.4
C(6)-C(7)-C(8)	121.26(16)
C(8)-C(7)-H(7)	119.4
C(18)-C(13)-C(14)	118.66(15)
C(18)-C(13)-C(2)	122.53(15)
C(14)-C(13)-C(2)	118.77(15)
N(1)-C(2)-C(13)	110.90(13)
N(1)-C(2)-C(3)	103.10(12)
N(2)-C(2)-N(1)	114.06(13)
N(2)-C(2)-C(13)	112.41(13)
N(2)-C(2)-C(3)	102.97(12)
C(13)-C(2)-C(3)	112.80(13)

N(1)-C(1)-H(1A)	109.5
N(1)-C(1)-H(1B)	109.5
N(1)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
O(1)-C(3)-C(4)	113.47(13)
O(1)-C(3)-C(2)	114.87(13)
O(1)-C(3)-C(12)	107.17(13)
C(4)-C(3)-C(2)	103.14(12)
C(4)-C(3)-C(12)	113.99(13)
C(12)-C(3)-C(2)	103.96(12)
C(18)-C(17)-H(17)	119.8
C(16)-C(17)-C(18)	120.36(17)
C(16)-C(17)-H(17)	119.8
C(9)-C(8)-H(8)	120.9
C(7)-C(8)-C(9)	118.23(15)
C(7)-C(8)-H(8)	120.9
N(2)-C(11)-H(11A)	111.4
N(2)-C(11)-H(11B)	111.4
N(2)-C(11)-C(12)	101.85(13)
H(11A)-C(11)-H(11B)	109.3
C(12)-C(11)-H(11A)	111.4
C(12)-C(11)-H(11B)	111.4
C(3)-C(12)-H(12A)	111.0
C(3)-C(12)-H(12B)	111.0
C(11)-C(12)-C(3)	103.85(13)
C(11)-C(12)-H(12A)	111.0
C(11)-C(12)-H(12B)	111.0
H(12A)-C(12)-H(12B)	109.0
N(2)-C(10)-H(10A)	109.5
N(2)-C(10)-H(10B)	109.5
N(2)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table S4. Anisotropic displacement parameters ($Å^2$x 10^3) for v18441_a. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	22(1)	14(1)	22(1)	-3(1)	4(1)	2(1)
N(1)	15(1)	14(1)	20(1)	-2(1)	4(1)	-1(1)
N(2)	22(1)	22(1)	16(1)	2(1)	1(1)	-4(1)
C(9)	13(1)	17(1)	13(1)	-1(1)	-2(1)	0(1)
C(6)	20(1)	22(1)	18(1)	1(1)	3(1)	-5(1)
C(5)	15(1)	19(1)	19(1)	-2(1)	2(1)	1(1)
C(18)	22(1)	17(1)	21(1)	-2(1)	5(1)	-1(1)
C(15)	17(1)	27(1)	19(1)	-6(1)	1(1)	3(1)
C(16)	16(1)	26(1)	28(1)	-12(1)	4(1)	-4(1)
C(4)	14(1)	13(1)	14(1)	-1(1)	-2(1)	0(1)
C(14)	17(1)	17(1)	20(1)	-1(1)	2(1)	0(1)
C(7)	23(1)	15(1)	18(1)	1(1)	-2(1)	-3(1)
C(13)	14(1)	16(1)	19(1)	-3(1)	4(1)	0(1)
C(2)	16(1)	15(1)	16(1)	0(1)	2(1)	0(1)
C(1)	17(1)	22(1)	30(1)	-4(1)	7(1)	0(1)
C(3)	15(1)	14(1)	17(1)	0(1)	2(1)	1(1)
C(17)	24(1)	21(1)	30(1)	-7(1)	9(1)	-7(1)
C(8)	17(1)	15(1)	18(1)	-2(1)	-2(1)	2(1)
C(11)	24(1)	26(1)	18(1)	5(1)	-4(1)	-3(1)
C(12)	19(1)	21(1)	24(1)	7(1)	-3(1)	3(1)
C(10)	31(1)	34(1)	18(1)	-1(1)	7(1)	-8(1)

Table S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for v18441_a.

	x	y	z	U(eq)

H(6)	7403	8221	817	24
H(5)	7263	5491	1303	21
H(18)	1334	1435	3528	24
H(15)	-1045	3616	-95	25
H(16)	-2217	1277	610	28
H(14)	1209	4928	1053	22
H(7)	5271	9976	1312	23
H(1A)	1208	7577	3790	34
H(1B)	259	5903	3494	34
H(1C)	521	7125	2448	34
H(17)	-997	178	2414	29
H(8)	3000	9062	2319	20
H(11A)	5709	3289	5368	28
H(11B)	5410	5074	4844	28
H(12A)	6224	2271	3548	26
H(12B)	7194	3973	3565	26
H(10A)	2417	5151	5351	41
H(10B)	2628	3401	5918	41
H(10C)	1093	3763	4884	41
H(1)	4270(40)	3250(40)	970(30)	41

Table S6. Torsion angles [°] for v18441_a.

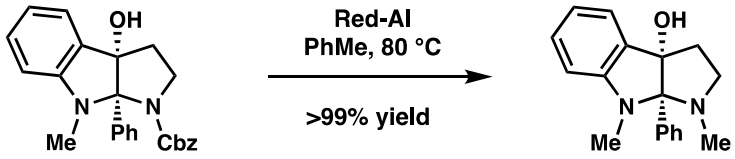
O(1)-C(3)-C(12)-C(11)	-142.05(14)
N(1)-C(9)-C(4)-C(5)	-177.39(14)
N(1)-C(9)-C(4)-C(3)	1.81(18)
N(1)-C(9)-C(8)-C(7)	176.94(15)
N(1)-C(2)-C(3)-O(1)	-131.12(14)
N(1)-C(2)-C(3)-C(4)	-7.13(15)
N(1)-C(2)-C(3)-C(12)	112.10(14)
N(2)-C(2)-C(3)-O(1)	109.98(15)
N(2)-C(2)-C(3)-C(4)	-126.02(13)
N(2)-C(2)-C(3)-C(12)	-6.79(16)
N(2)-C(11)-C(12)-C(3)	39.90(17)
C(9)-N(1)-C(2)-N(2)	119.65(14)

C(9)-N(1)-C(2)-C(13)	-112.21(15)
C(9)-N(1)-C(2)-C(3)	8.77(16)
C(9)-C(4)-C(3)-O(1)	128.51(14)
C(9)-C(4)-C(3)-C(2)	3.60(16)
C(9)-C(4)-C(3)-C(12)	-108.43(15)
C(6)-C(5)-C(4)-C(9)	-0.3(2)
C(6)-C(5)-C(4)-C(3)	-179.31(15)
C(6)-C(7)-C(8)-C(9)	1.0(2)
C(5)-C(6)-C(7)-C(8)	0.7(2)
C(5)-C(4)-C(3)-O(1)	-52.4(2)
C(5)-C(4)-C(3)-C(2)	-177.28(15)
C(5)-C(4)-C(3)-C(12)	70.7(2)
C(18)-C(13)-C(2)-N(1)	-140.28(15)
C(18)-C(13)-C(2)-N(2)	-11.3(2)
C(18)-C(13)-C(2)-C(3)	104.65(18)
C(15)-C(16)-C(17)-C(18)	0.8(3)
C(15)-C(14)-C(13)-C(18)	1.0(2)
C(15)-C(14)-C(13)-C(2)	178.65(15)
C(16)-C(15)-C(14)-C(13)	1.3(2)
C(4)-C(9)-C(8)-C(7)	-2.4(2)
C(4)-C(3)-C(12)-C(11)	91.52(16)
C(14)-C(15)-C(16)-C(17)	-2.2(2)
C(14)-C(13)-C(2)-N(1)	42.1(2)
C(14)-C(13)-C(2)-N(2)	171.16(14)
C(14)-C(13)-C(2)-C(3)	-72.94(19)
C(7)-C(6)-C(5)-C(4)	-1.1(2)
C(13)-C(18)-C(17)-C(16)	1.5(3)
C(13)-C(2)-C(3)-O(1)	-11.44(19)
C(13)-C(2)-C(3)-C(4)	112.56(14)
C(13)-C(2)-C(3)-C(12)	-128.21(14)
C(2)-N(1)-C(9)-C(4)	-7.06(18)
C(2)-N(1)-C(9)-C(8)	173.58(15)
C(2)-N(2)-C(11)-C(12)	-46.46(17)
C(2)-C(3)-C(12)-C(11)	-20.02(16)
C(1)-N(1)-C(9)-C(4)	-162.46(14)
C(1)-N(1)-C(9)-C(8)	18.2(2)

C(1)-N(1)-C(2)-N(2)	-86.00(19)
C(1)-N(1)-C(2)-C(13)	42.1(2)
C(1)-N(1)-C(2)-C(3)	163.12(14)
C(17)-C(18)-C(13)-C(14)	-2.3(2)
C(17)-C(18)-C(13)-C(2)	-179.94(15)
C(8)-C(9)-C(4)-C(5)	2.0(2)
C(8)-C(9)-C(4)-C(3)	-178.77(13)
C(11)-N(2)-C(2)-N(1)	-78.14(17)
C(11)-N(2)-C(2)-C(13)	154.50(14)
C(11)-N(2)-C(2)-C(3)	32.81(17)
C(10)-N(2)-C(2)-N(1)	49.8(2)
C(10)-N(2)-C(2)-C(13)	-77.58(18)
C(10)-N(2)-C(2)-C(3)	160.74(14)
C(10)-N(2)-C(11)-C(12)	-176.45(15)

Symmetry transformations used to generate equivalent atoms:

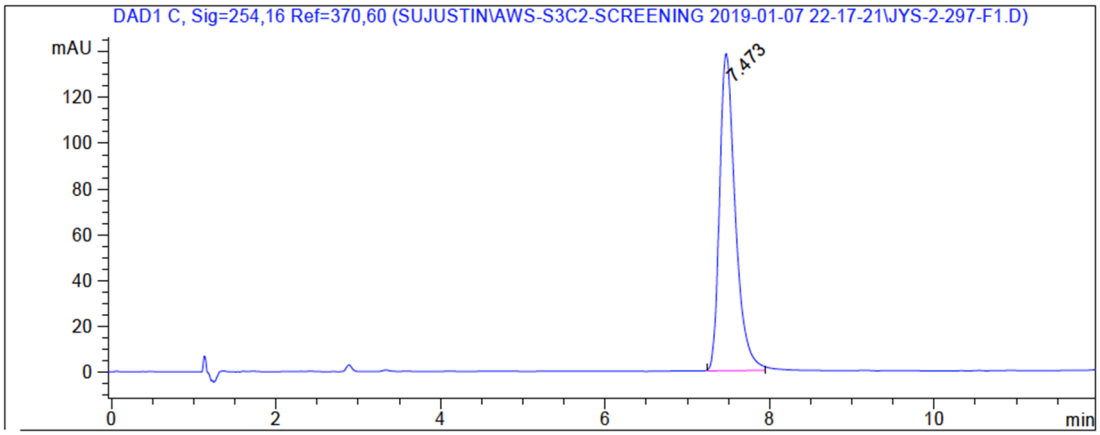
Absolute Stereochemical Assignment of (+)-6:



(+)-6 (+)-2

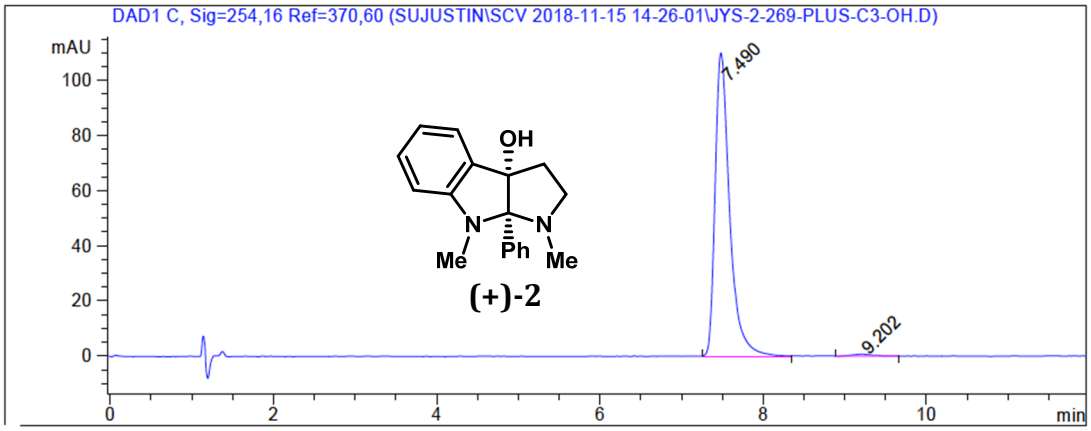
A 1 dram vial was charged with (+)-**6** (5 mg, 12 µmol) and PhMe (250 µL). Red-Al (60 wt% in PhMe, 32 µL, 99 µmol, 8.0 equiv) was added dropwise. After stirring at ambient temperature for 5 min, the vial was flushed with argon and sealed with a Teflon cap. The reaction was then stirred at 80 °C for 2.5 h. The reaction was cooled to room temperature and then quenched slowly with 1 M aqueous solution of Rochelle's salt (0.5 mL). The resulting mixture was stirred for 1 h and then extracted with Et_2O (1 mL x 4) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10–20% EtOAc/hexanes) to afford (+)-**2** (3.5 mg, quant yield) as a yellow solid. The ^1H NMR spectrum and chiral SFC trace were consistent with those of (+)-**2**.

Chiral SFC trace for product of Red-Al reduction of (+)-6 (15% *i*-PrOH/CO_2):



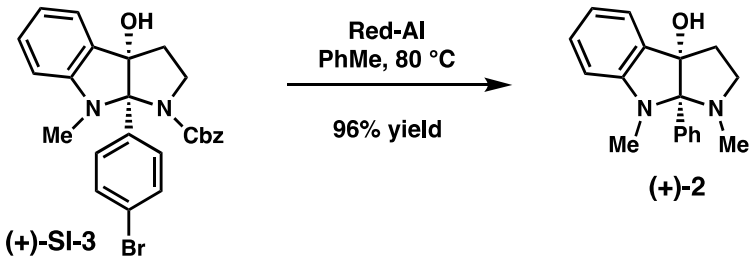
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.473	BB	0.2030	1840.90125	138.51805	100.0000

Chiral SFC trace for (+)-2 (15% *i*-PrOH/CO_2):



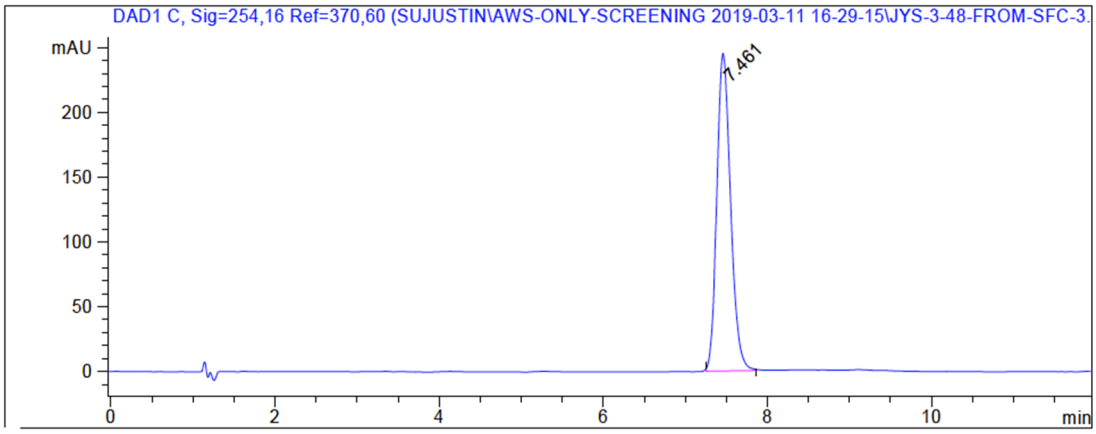
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.490	BB	0.1964	1367.62573	107.52038	98.9857
2	9.202	BB	0.2948	14.01365	7.08409e-1	1.0143

Absolute Stereochemical Assignment of (+)-SI-3:



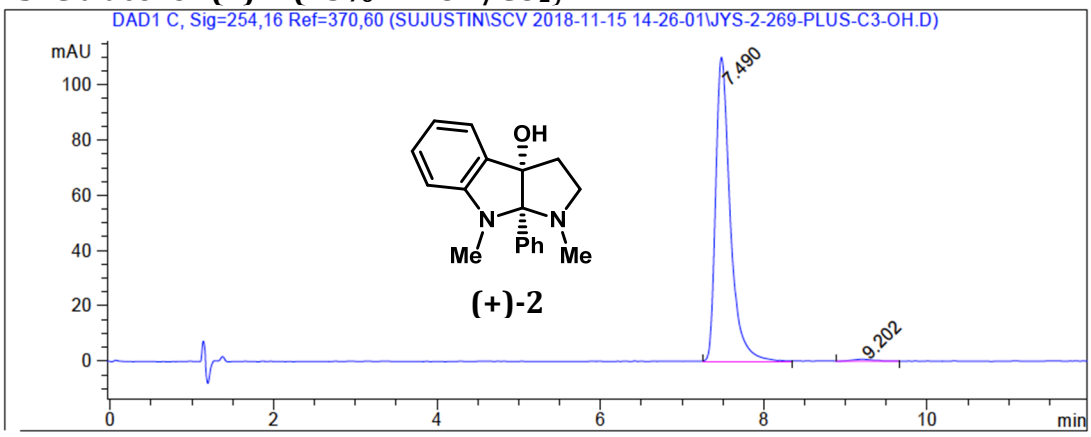
A 25 mL round-bottom flask was charged with (+)-**SI-3** (50 mg, 104 µmol) and PhMe (2.1 mL). Red-Al (60 wt% in PhMe, 270 µL, 834 µmol, 8.0 equiv) was added dropwise. After stirring at ambient temperature for 5 min, the vial was flushed with argon and sealed with a Teflon cap. The reaction was then stirred at 80 °C for 2.5 h. The reaction was cooled to room temperature and then quenched slowly with 1 M aqueous solution of Rochelle's salt (2.5 mL). The resulting mixture was stirred for 1 h and then extracted with Et_2O (4 mL x 4) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10–20% EtOAc/hexanes) to afford (+)-**2** (28 mg, 96% yield) as a yellow solid. The ^{1}H NMR spectrum and chiral SFC trace were consistent with those of (+)-**2**.

Chiral SFC trace for product of Red-Al reduction of (+)-SI-3 (15% *i*-PrOH/CO_2):



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.461	BB	0.1802	2857.55933	244.83841	100.0000

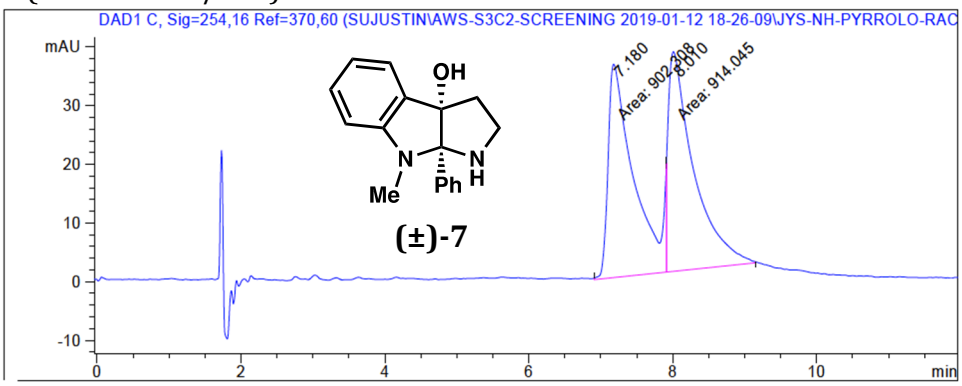
Chiral SFC trace for (+)-2 (15% *i*-PrOH/CO_2):



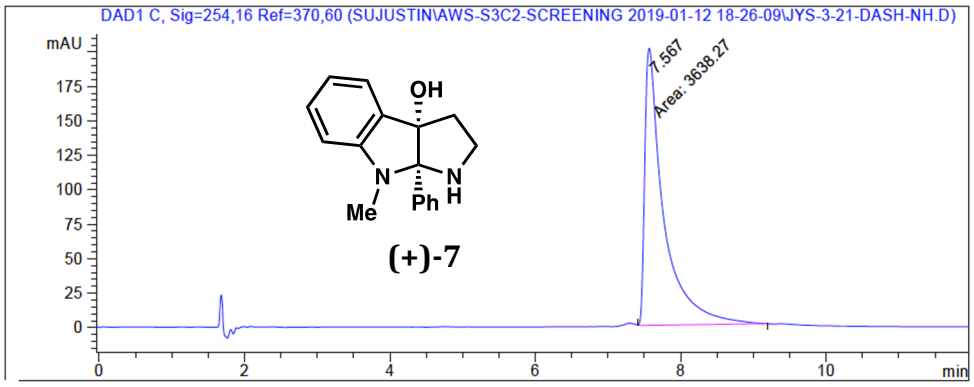
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.490	BB	0.1964	1367.62573	107.52038	98.9857
2	9.202	BB	0.2948	14.01365	7.08409e-1	1.0143

6. Chiral SFC Traces for Compounds 7–15, SI-4, 16

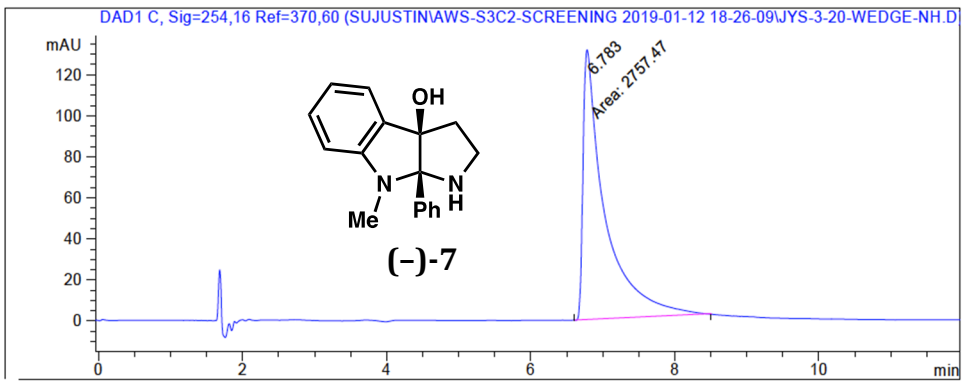
7 (30% *i*-PrOH/CO_2)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.180	MF	0.4125	902.30786	36.45488	49.6769
2	8.010	FM	0.4063	914.04492	37.49168	50.3231

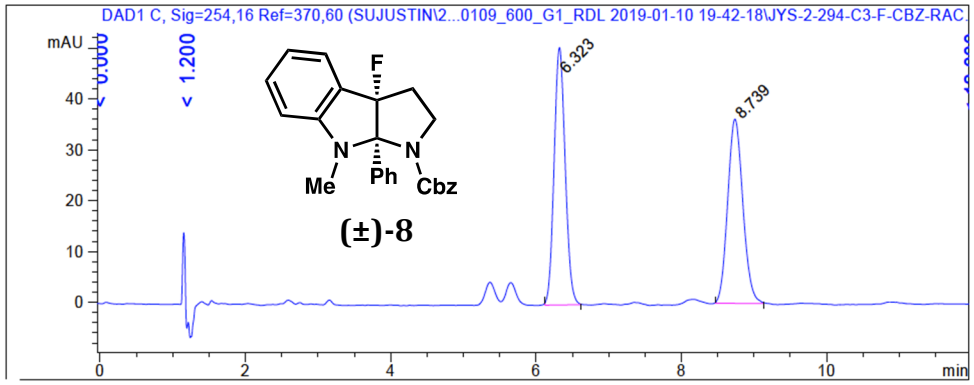


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.567	MM	0.3014	3638.27319	201.17644	100.0000

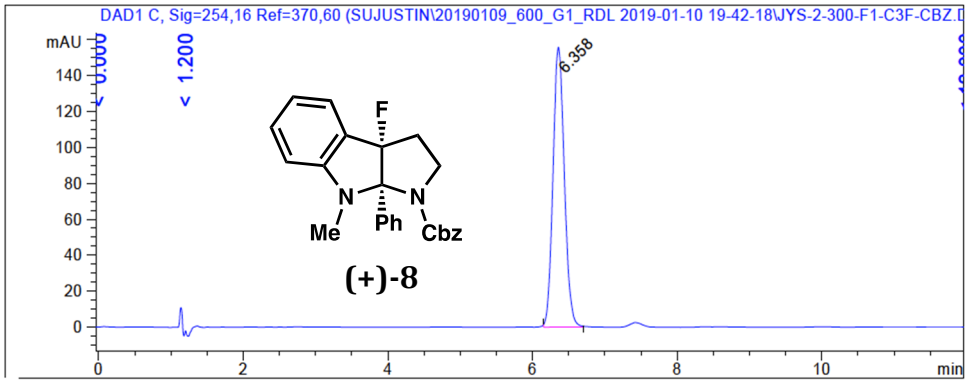


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.783	MM	0.3492	2757.47290	131.62311	100.0000

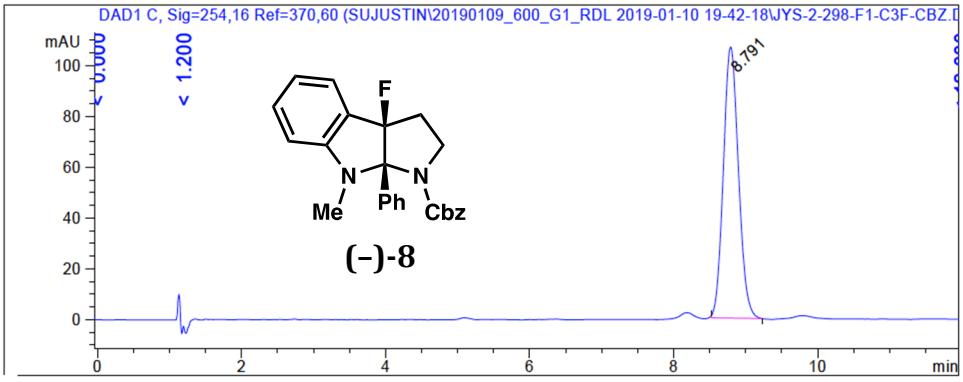
8 (20% *i*-PrOH/CO_2)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.323	BB	0.1639	536.97345	50.56442	50.5045
2	8.739	BB	0.2255	526.24597	36.21258	49.4955

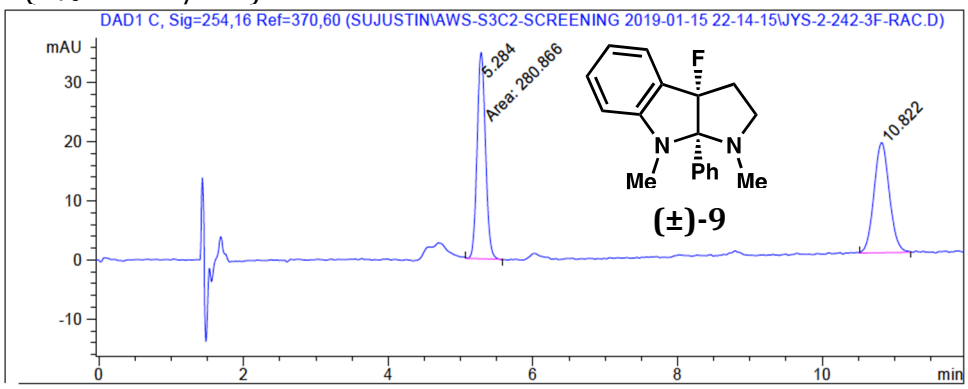


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.358	BB	0.1714	1701.10938	155.80974	100.0000

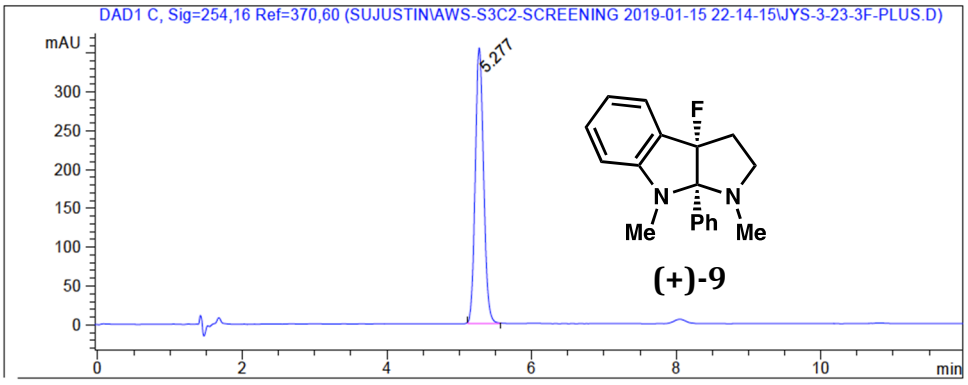


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.791	BB	0.2261	1556.85083	106.75185	100.0000

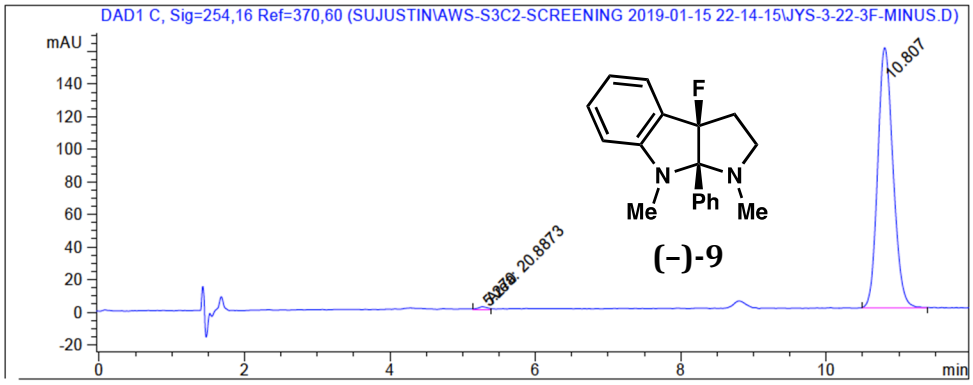
9 (5% *i*-PrOH/CO_2)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.284	MM	0.1339	280.86584	34.97139	50.4976
2	10.822	BB	0.2326	275.33075	18.60716	49.5024

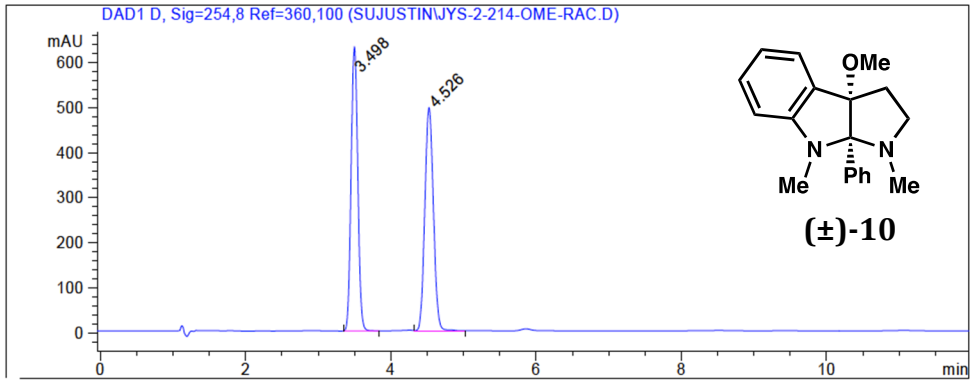


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.277	BB	0.1259	2854.18237	354.69470	100.0000

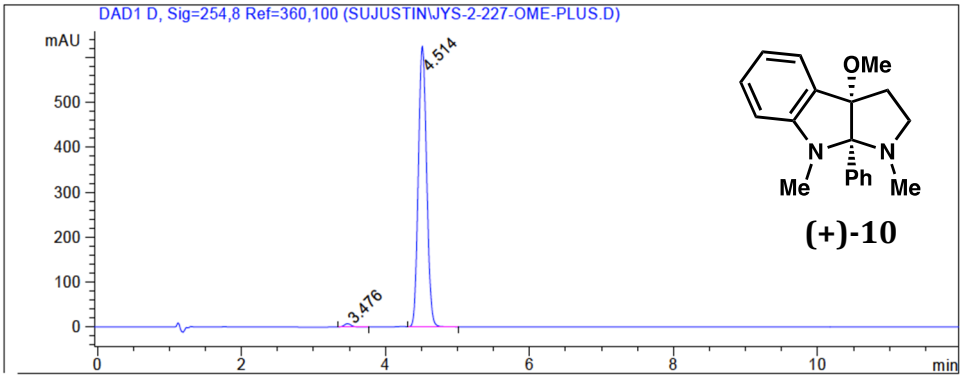


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.270	MM	0.1682	20.88730	2.06999	0.8821
2	10.807	BB	0.2274	2347.01172	159.77217	99.1179

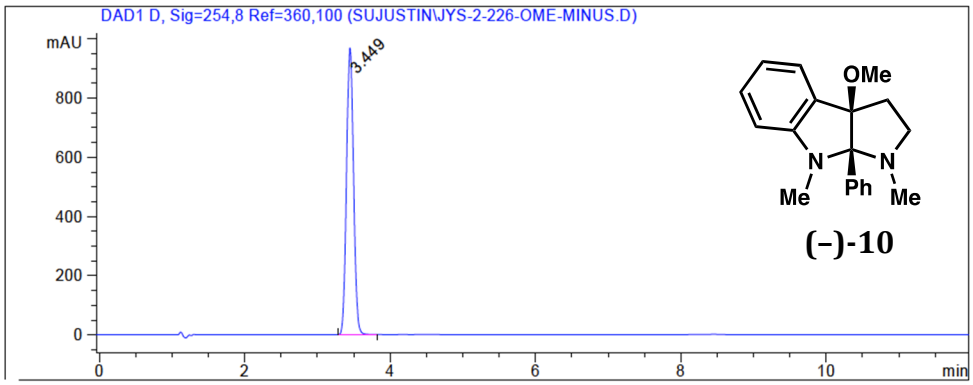
10 (10% *i*-PrOH/CO_2



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.498	BB	0.1028	4022.52856	627.68420	49.7231
2	4.526	VB	0.1280	4067.33813	494.28415	50.2769

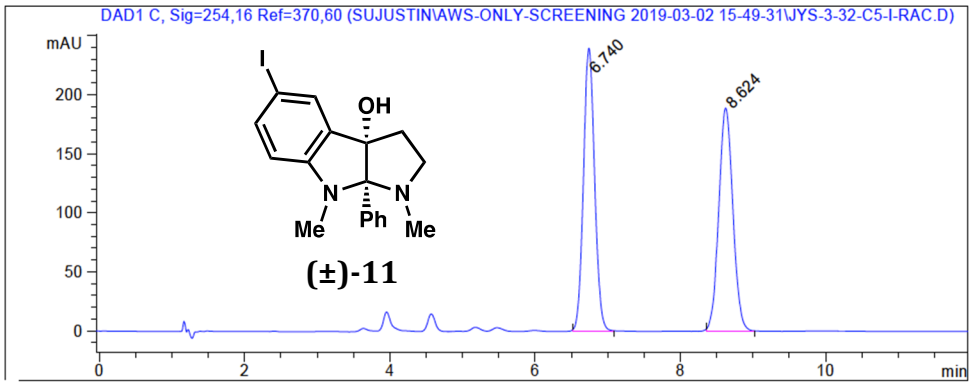


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.476	BB	0.1082	52.39898	7.61897	1.0328
2	4.514	VB	0.1257	5021.10645	624.99957	98.9672

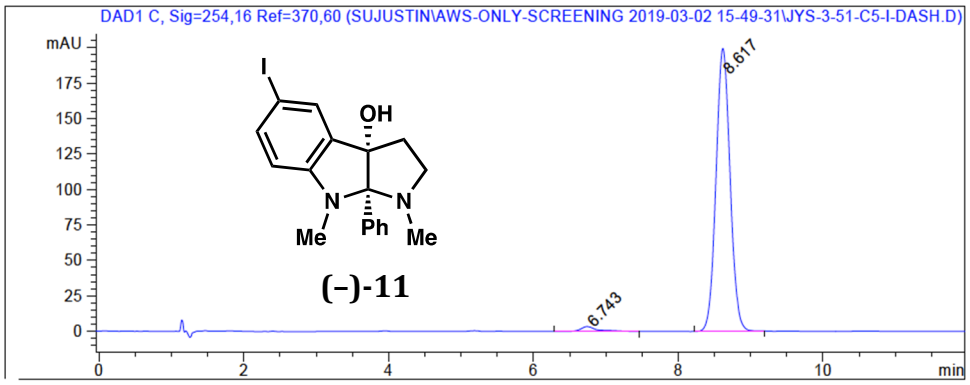


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.449	BB	0.1068	6534.56348	967.50690	100.0000

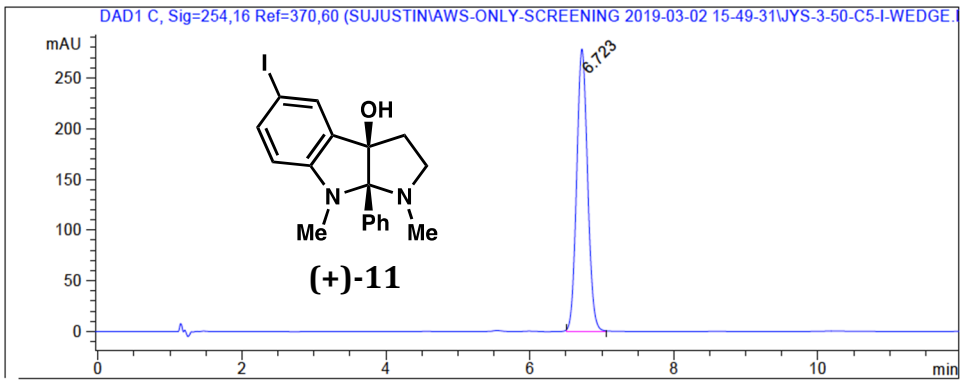
11 (25% *i*-PrOH/CO_2)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.740	BB	0.1651	2566.61060	239.42740	50.1429
2	8.624	BB	0.2096	2551.98022	188.85854	49.8571

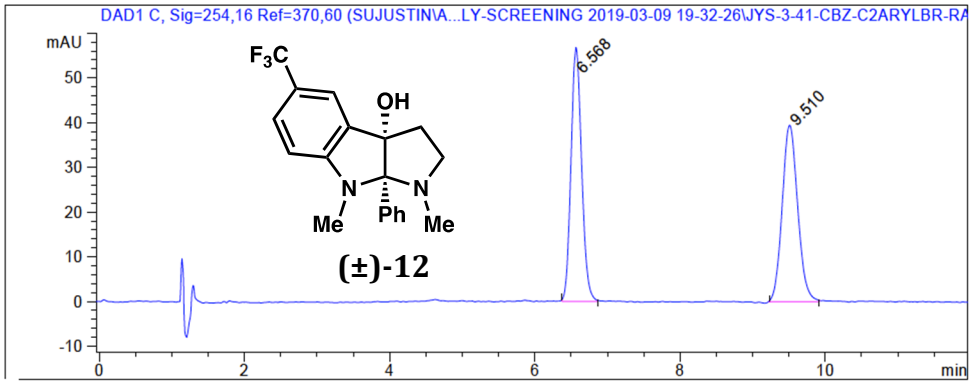


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.743	VV	0.2570	61.29403	3.55756	2.2123
2	8.617	BB	0.2104	2709.30859	199.54309	97.7877

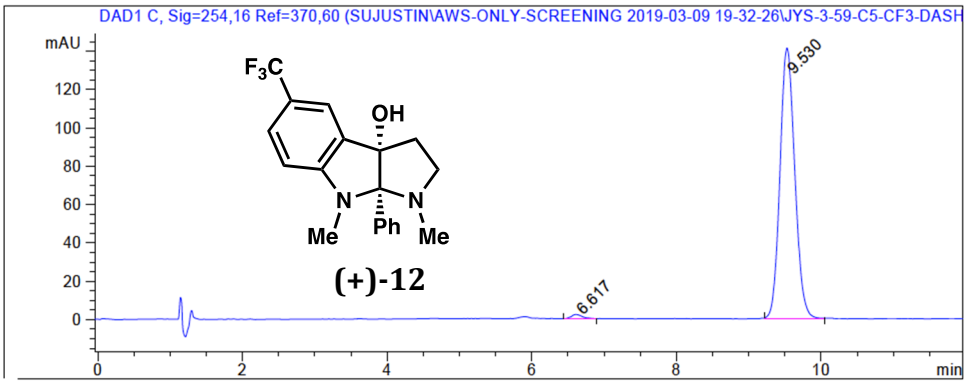


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.723	BB	0.1632	2939.69409	278.40146	100.0000

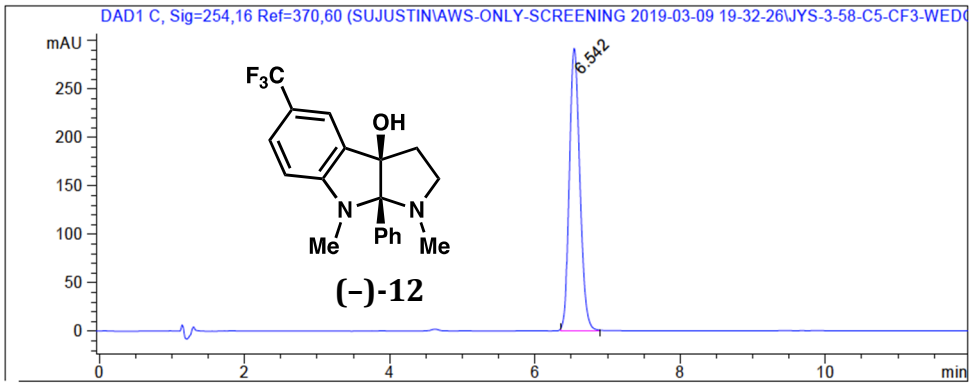
12 (10% *i*-PrOH/CO_2)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.568	BB	0.1591	578.54144	56.69032	49.7203
2	9.510	BB	0.2290	585.05115	39.45054	50.2797

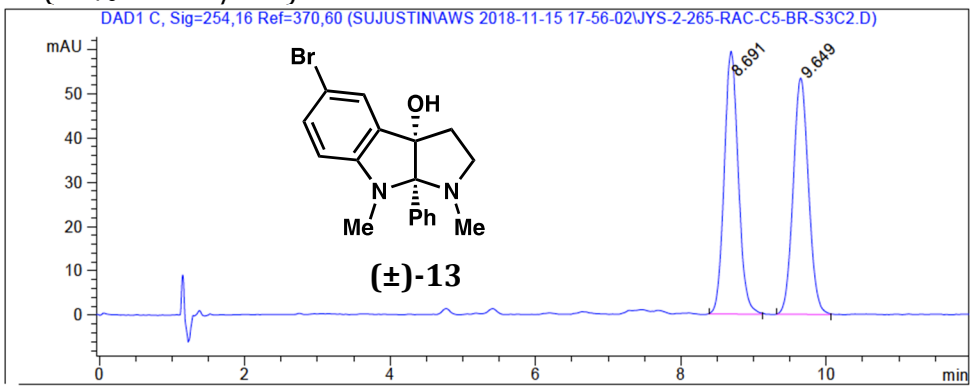


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.617	BB	0.1584	23.69976	2.18807	1.1645
2	9.530	BB	0.2222	2011.49292	141.22478	98.8355

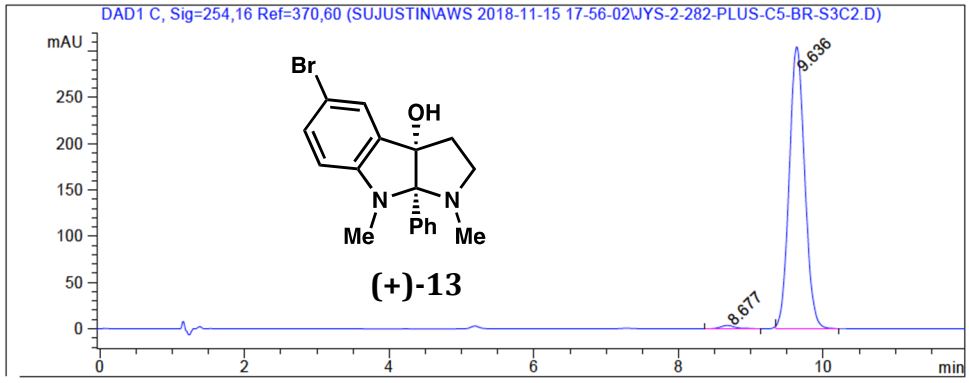


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.542	BB	0.1536	2933.63965	291.07697	100.0000

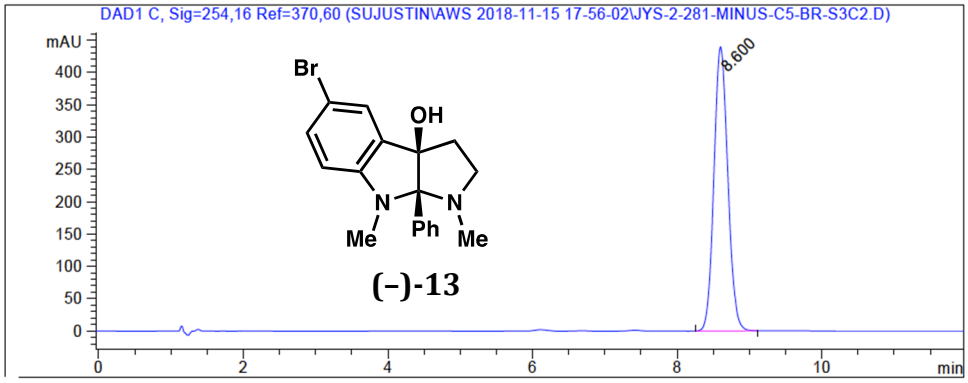
13 (20% *i*-PrOH/CO_2)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.691	BB	0.2089	797.96680	59.34822	50.5087
2	9.649	BB	0.2290	781.89453	53.34758	49.4913

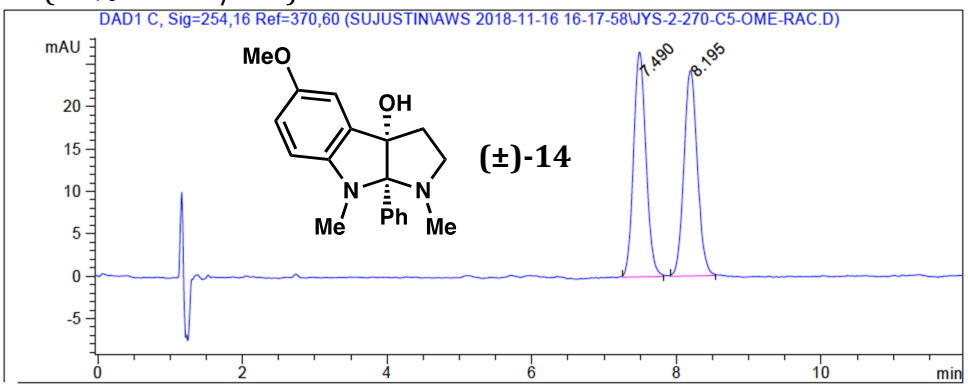


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.677	BB	0.2394	52.46638	3.49049	1.1431
2	9.636	BB	0.2401	4537.37256	300.54257	98.8569

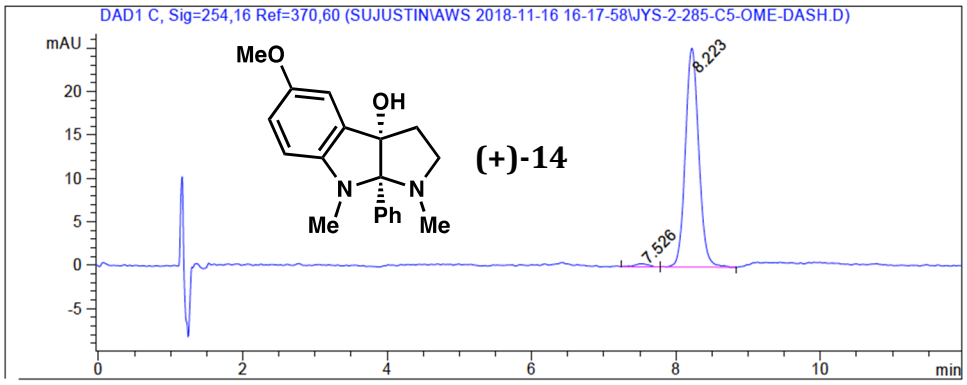


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.600	BB	0.2080	5878.18701	439.70908	100.0000

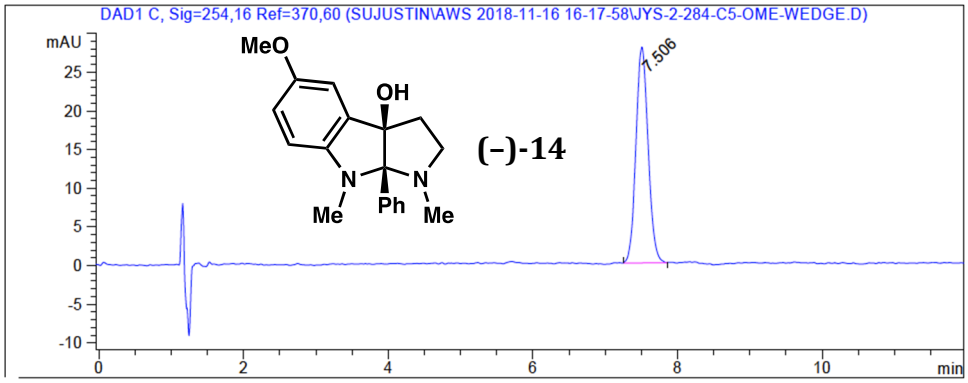
14 (20% *i*-PrOH/CO_2)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.490	BB	0.1836	317.64722	26.55142	50.2906
2	8.195	BB	0.1989	313.97678	24.27218	49.7094

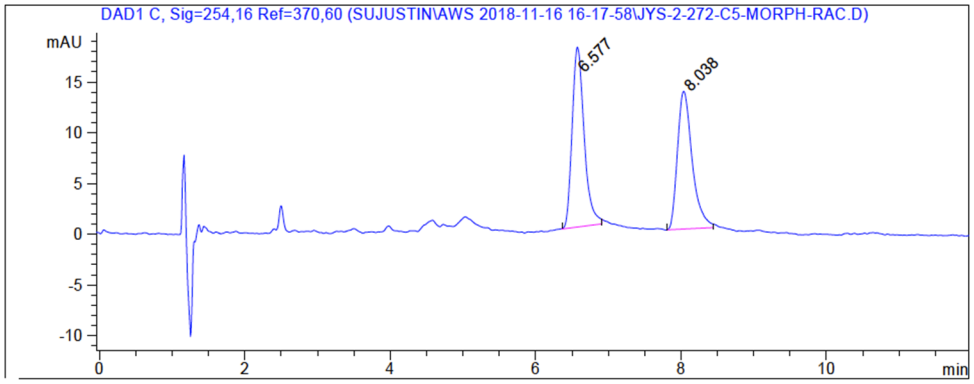


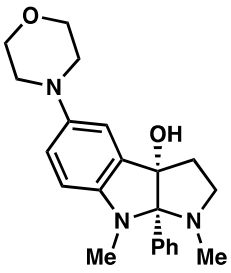
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.526	BV	0.2156	4.57488	3.34514e-1	1.3855
2	8.223	VB	0.2073	325.61078	25.10895	98.6145



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.506	BB	0.1846	326.73755	27.91238	100.0000

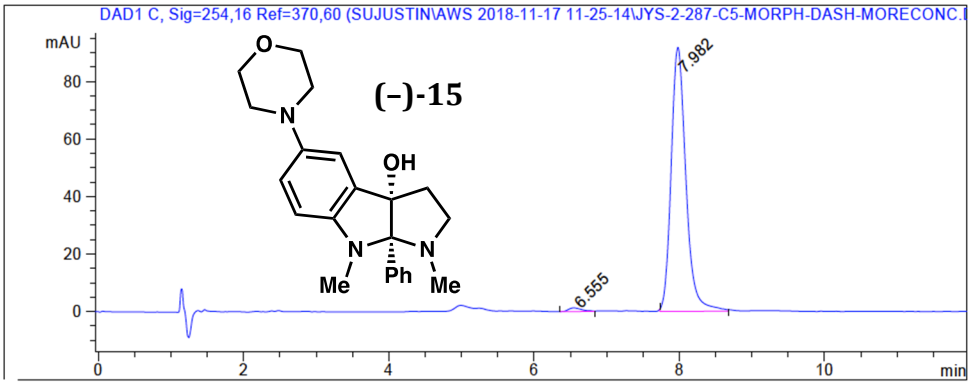
15 (25% *i*-PrOH/CO_2)



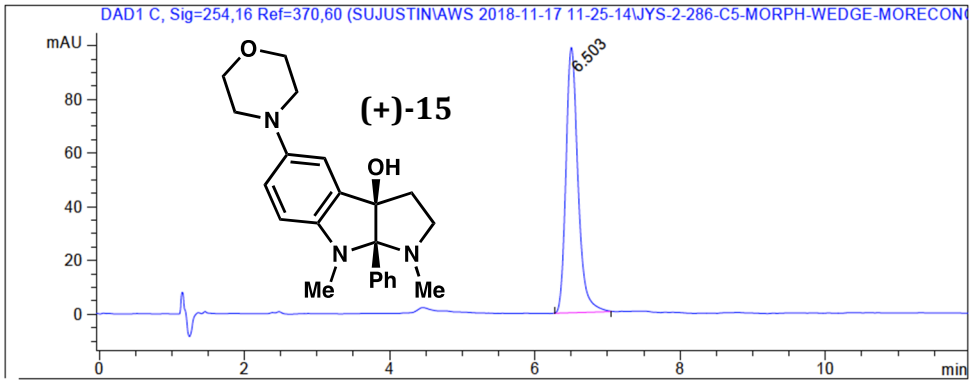


(±)-15

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.577	BB	0.1783	204.30373	17.74856	51.6194
2	8.038	BB	0.2184	191.48512	13.59089	48.3806

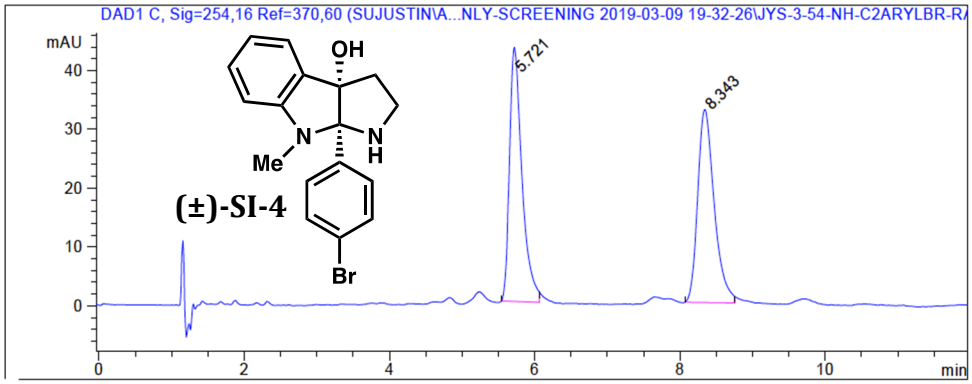


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.555	BB	0.1921	16.62105	1.27474	1.2666
2	7.982	BB	0.2214	1295.64758	91.37109	98.7334

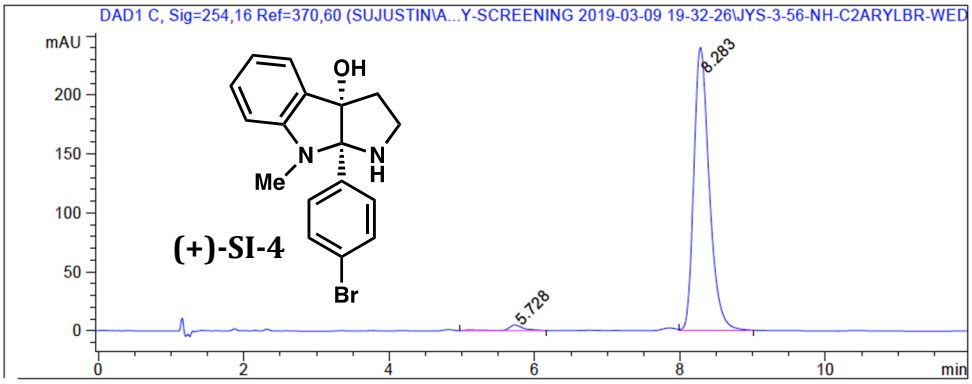


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.503	BB	0.1766	1139.51855	98.79003	100.0000

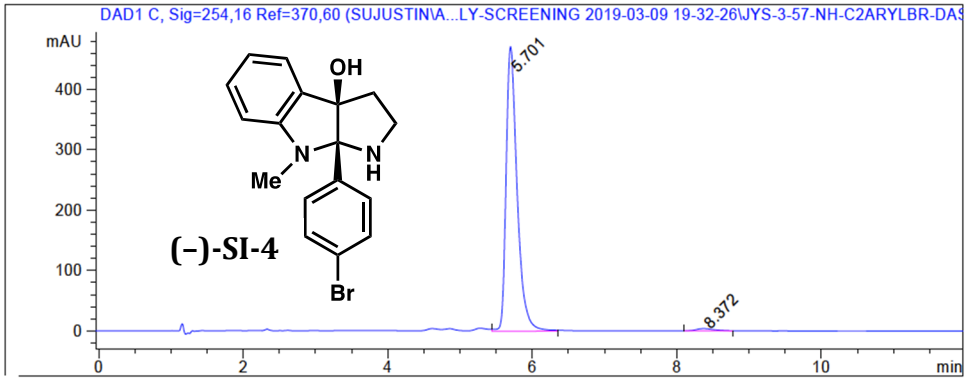
SI-4 (30% *i*-PrOH/CO_2)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.721	BB	0.1792	515.27948	43.17654	49.9178
2	8.343	BB	0.2400	516.97644	32.77376	50.0822

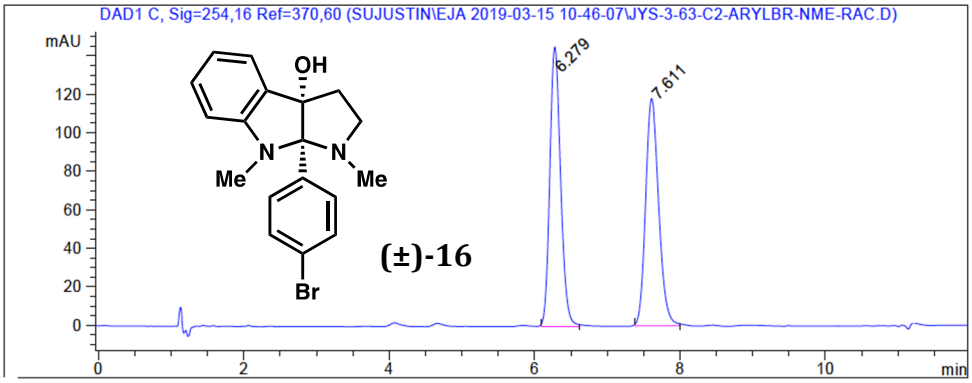


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.728	VB	0.2266	79.58464	4.97573	2.1871
2	8.283	VB	0.2250	3559.16260	240.06970	97.8129

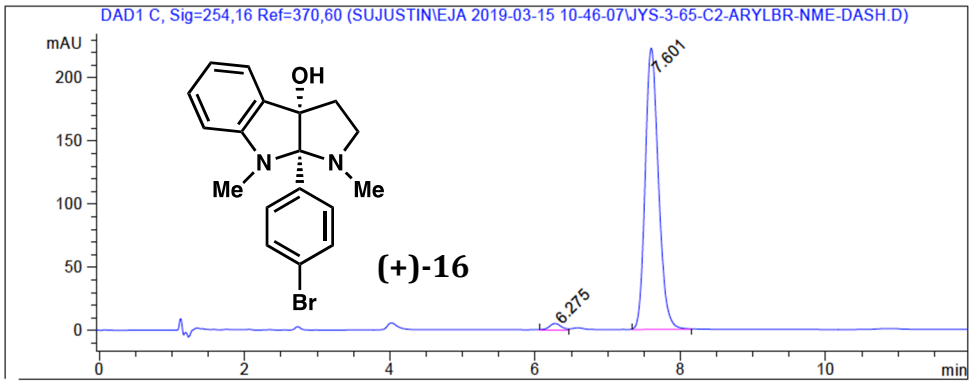


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.701	VB	0.1599	5004.51514	471.17020	98.7859
2	8.372	BB	0.2478	61.50673	3.74167	1.2141

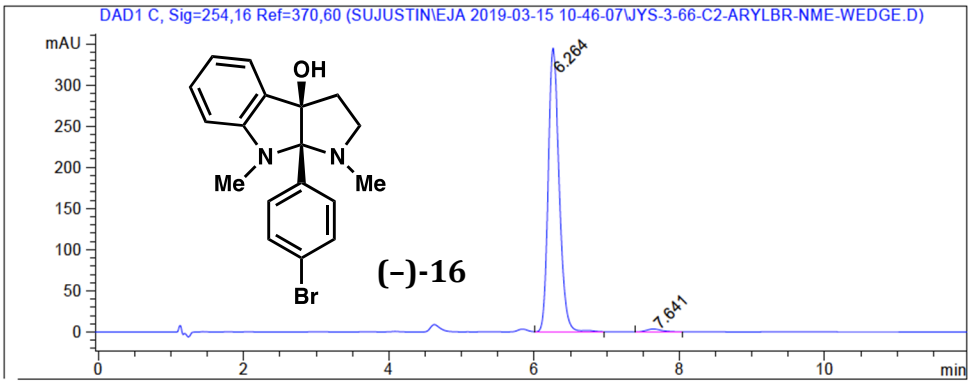
16 (25% *i*-PrOH/CO_2)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.279	BB	0.1602	1491.97437	144.81296	50.3005
2	7.611	BB	0.1939	1474.14539	117.91700	49.6995



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.275	BV	0.1662	52.66232	4.86733	1.8227
2	7.601	BB	0.1967	2836.63940	222.61716	98.1773



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.264	VB	0.1624	3610.23193	344.01962	98.5984
2	7.641	BB	0.2169	51.32042	3.54551	1.4016

7. References

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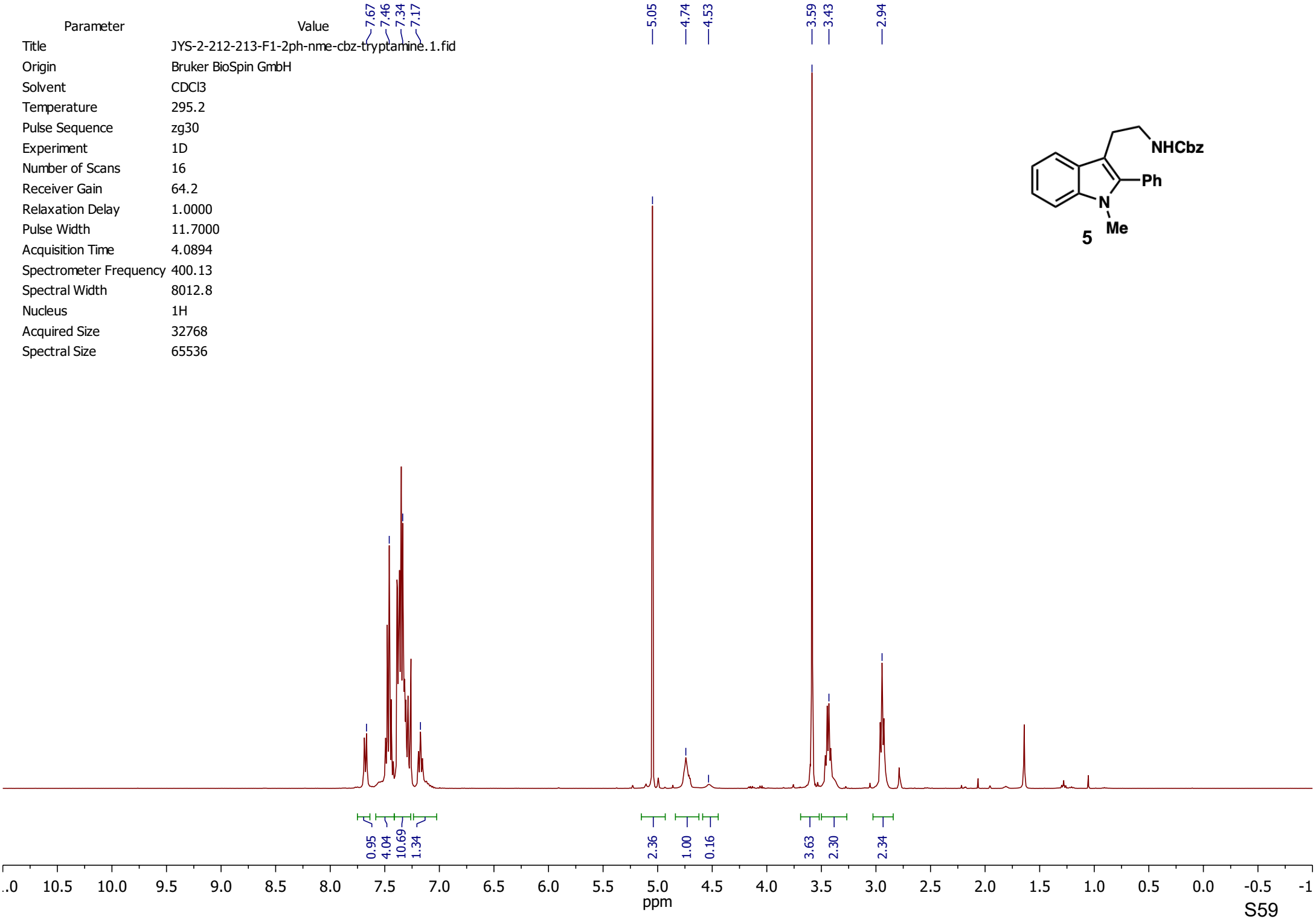
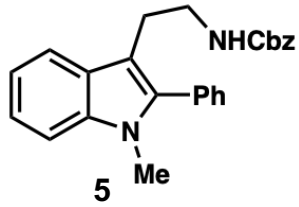
Parameter	Value
Title	JYS-2-212-213-F1-2ph-nme-cbz-tryptamine.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	64.2
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

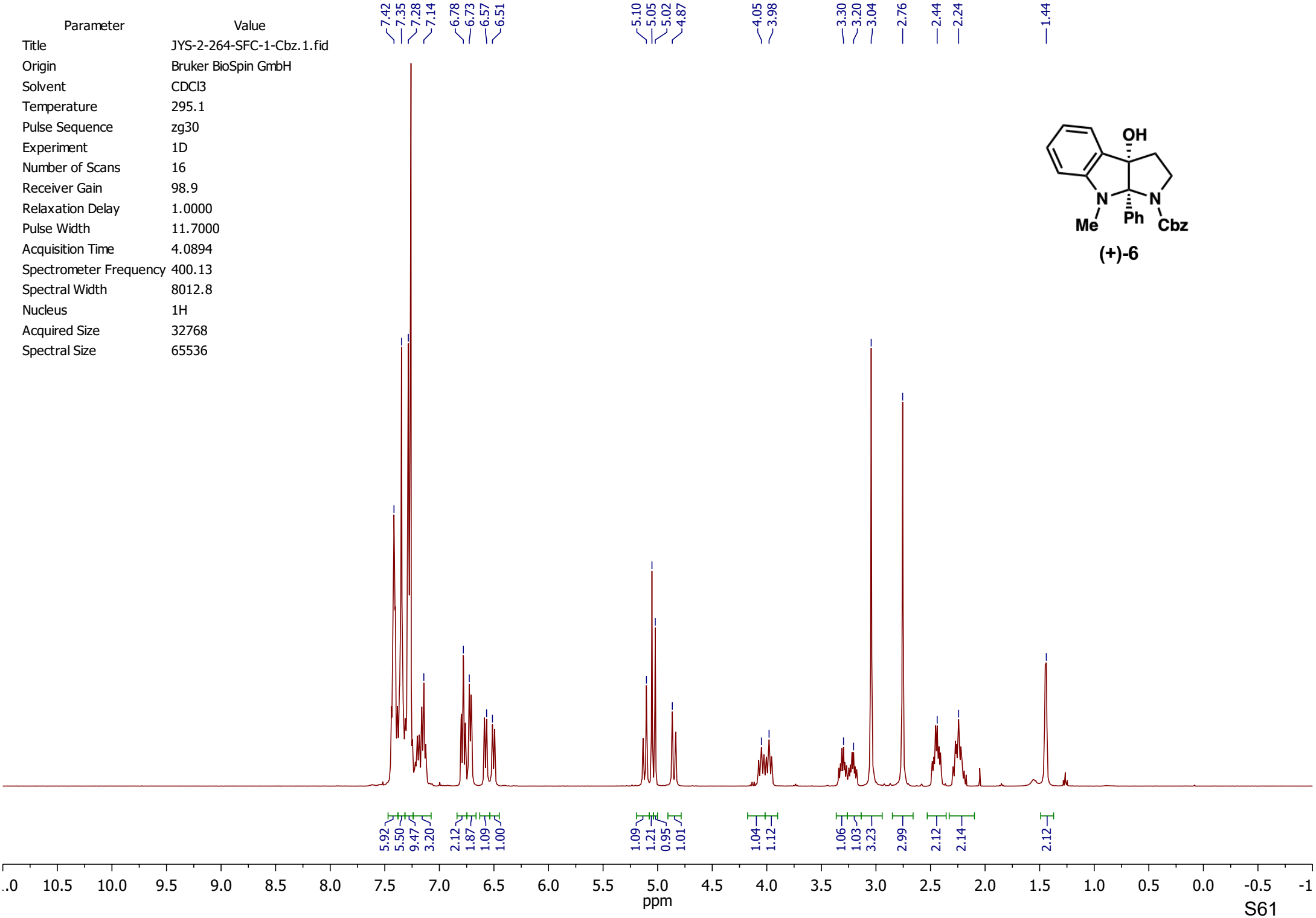


Parameter	Value
Title	JYS-2-212-213-F1-2ph-nme-cbz-tryptamine.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zgpg30
Experiment	1D
Probe	Z122623_0045 (CPP BBO 400S1 BB-H&F-D-05 Z)
Number of Scans	512
Receiver Gain	64.2
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

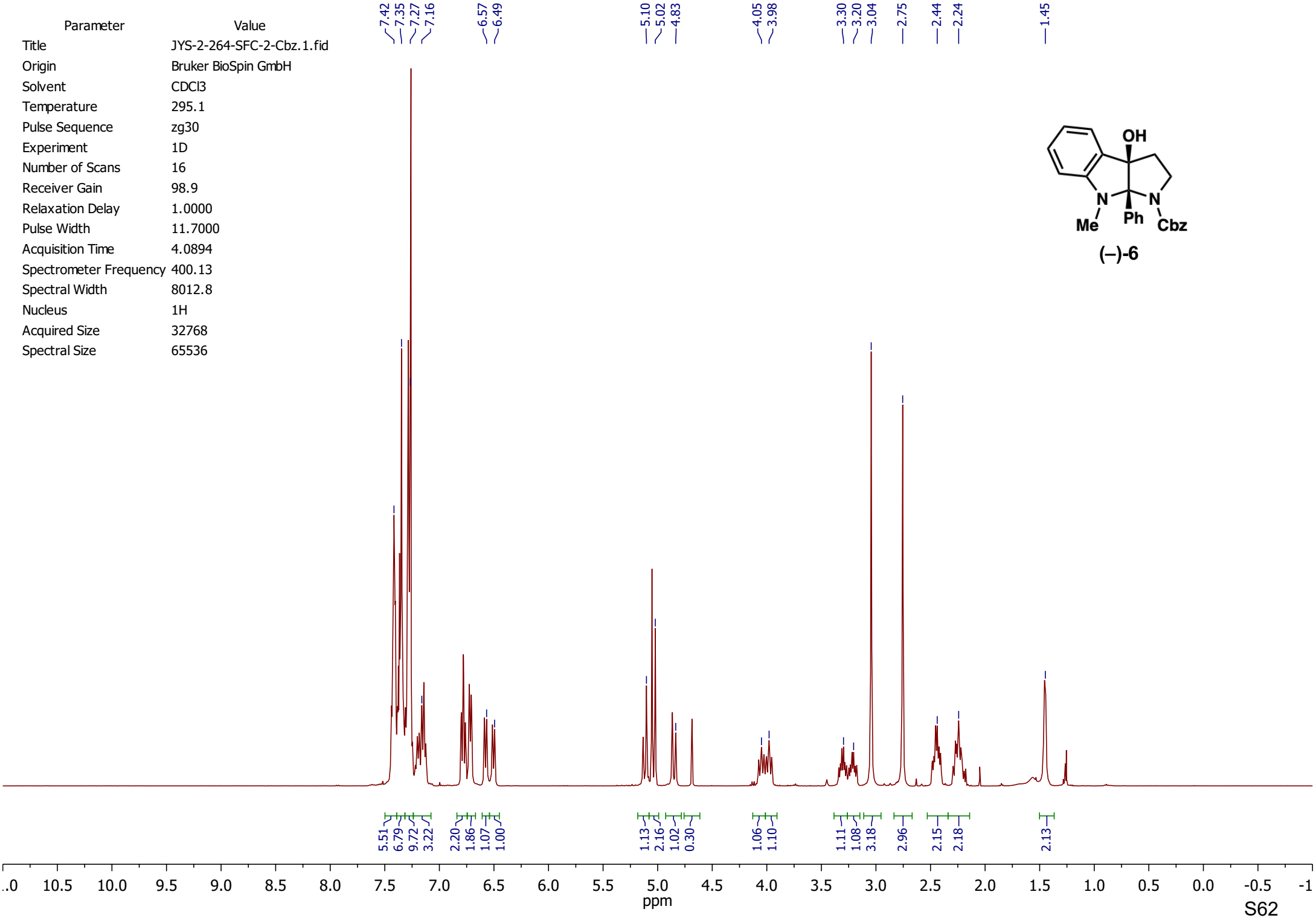


5

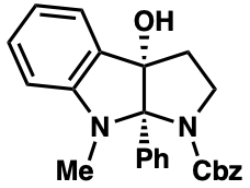
Parameter	Value
Title	JYS-2-264-SFC-1-Cbz.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	98.9
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



Parameter	Value
Title	JYS-2-264-SFC-2-Cbz.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	98.9
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



Parameter	Value
Title	JYS-2-264-SFC-1-Cbz.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	512
Receiver Gain	64.2
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



(+)-6

136.85
135.71
130.92
128.80
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127.52
127.46
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117.95
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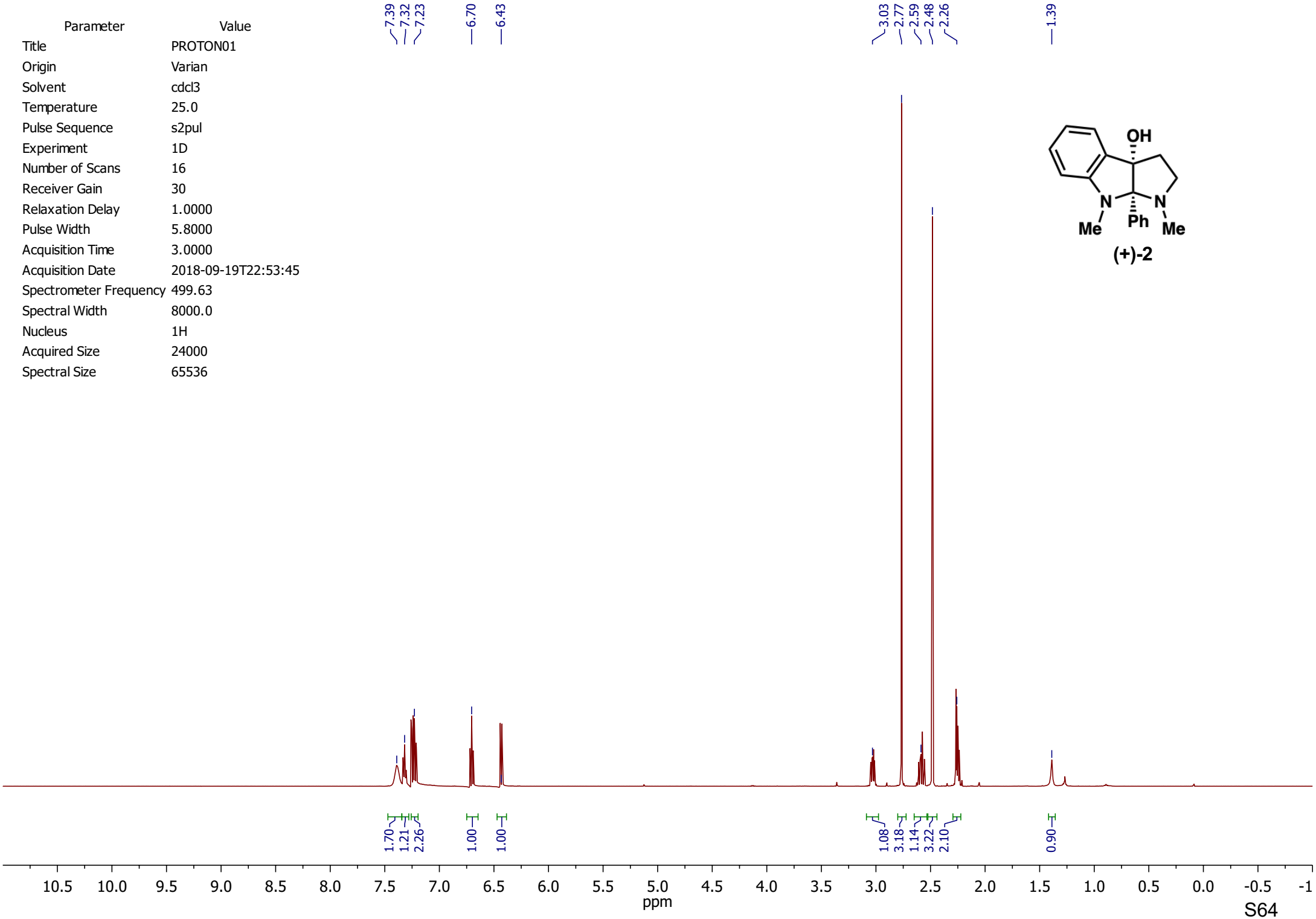
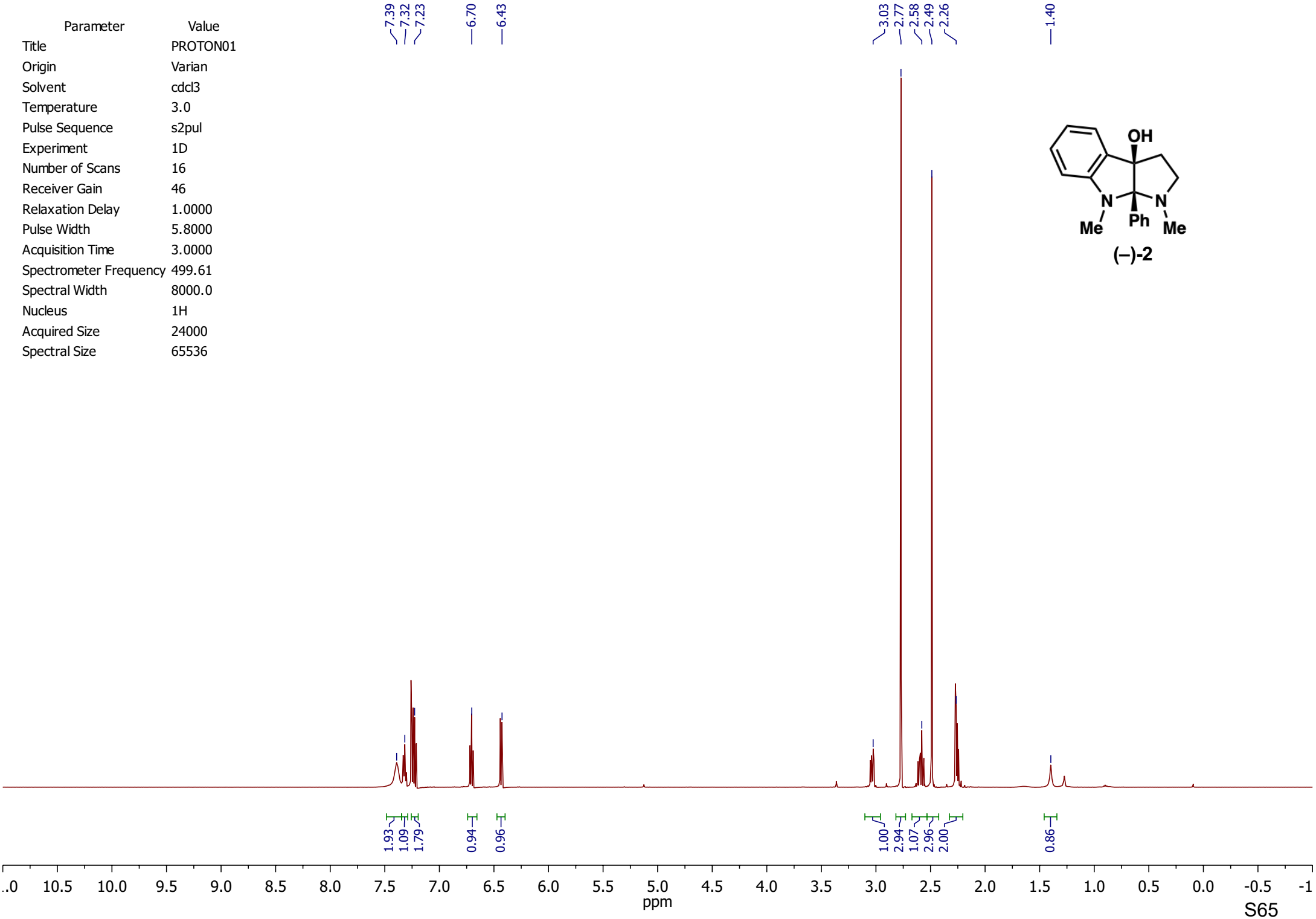
106.61
94.39
93.74
89.81
88.73
67.14
66.87
46.45
46.33
34.27
33.78
32.04
31.44

ppm

Parameter	Value
Title	PROTON01
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	5.8000
Acquisition Time	3.0000
Acquisition Date	2018-09-19T22:53:45
Spectrometer Frequency	499.63
Spectral Width	8000.0
Nucleus	1H
Acquired Size	24000
Spectral Size	65536



Parameter	Value
Title	PROTON01
Origin	Varian
Solvent	cdcl3
Temperature	3.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	46
Relaxation Delay	1.0000
Pulse Width	5.8000
Acquisition Time	3.0000
Spectrometer Frequency	499.61
Spectral Width	8000.0
Nucleus	1H
Acquired Size	24000
Spectral Size	65536



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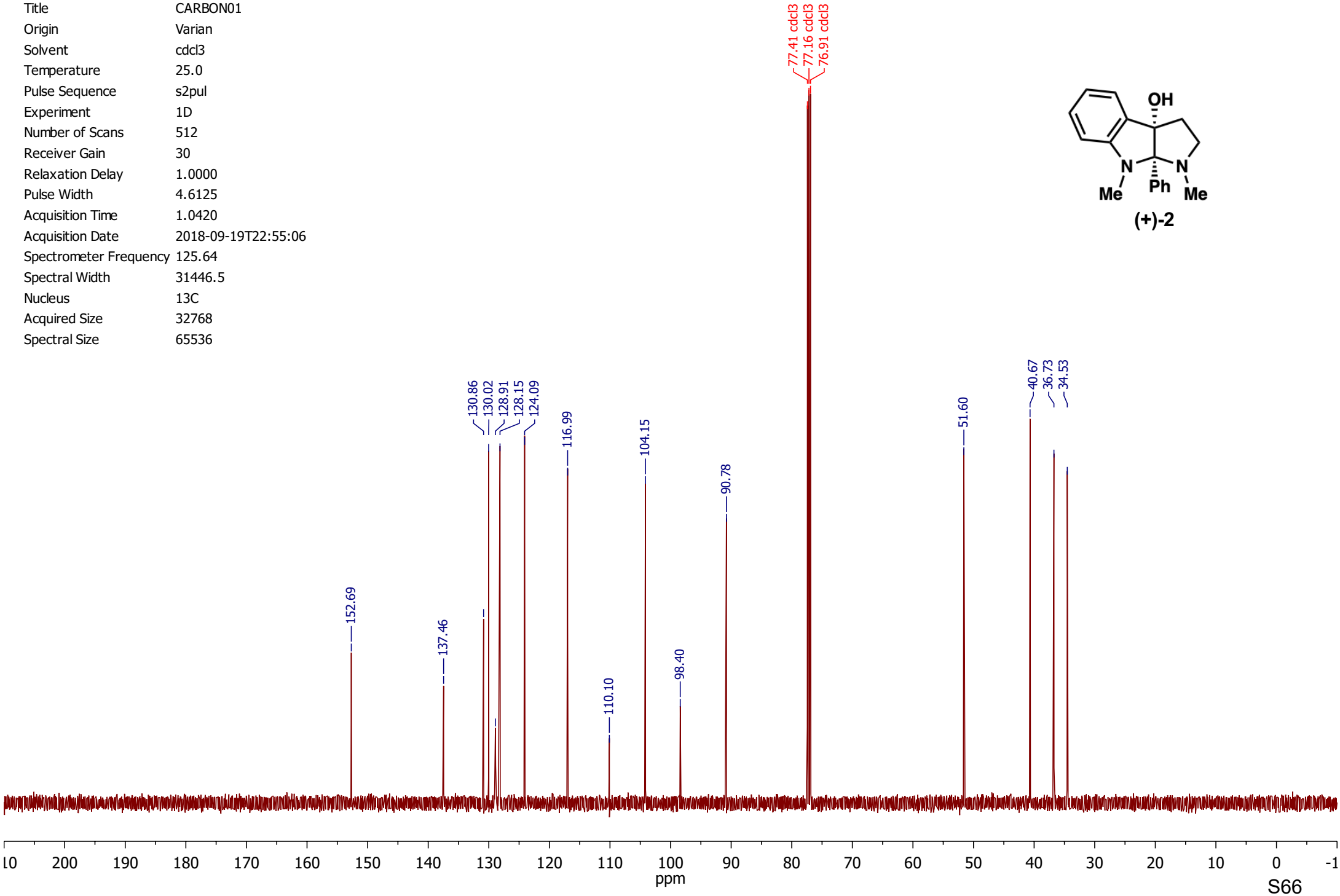
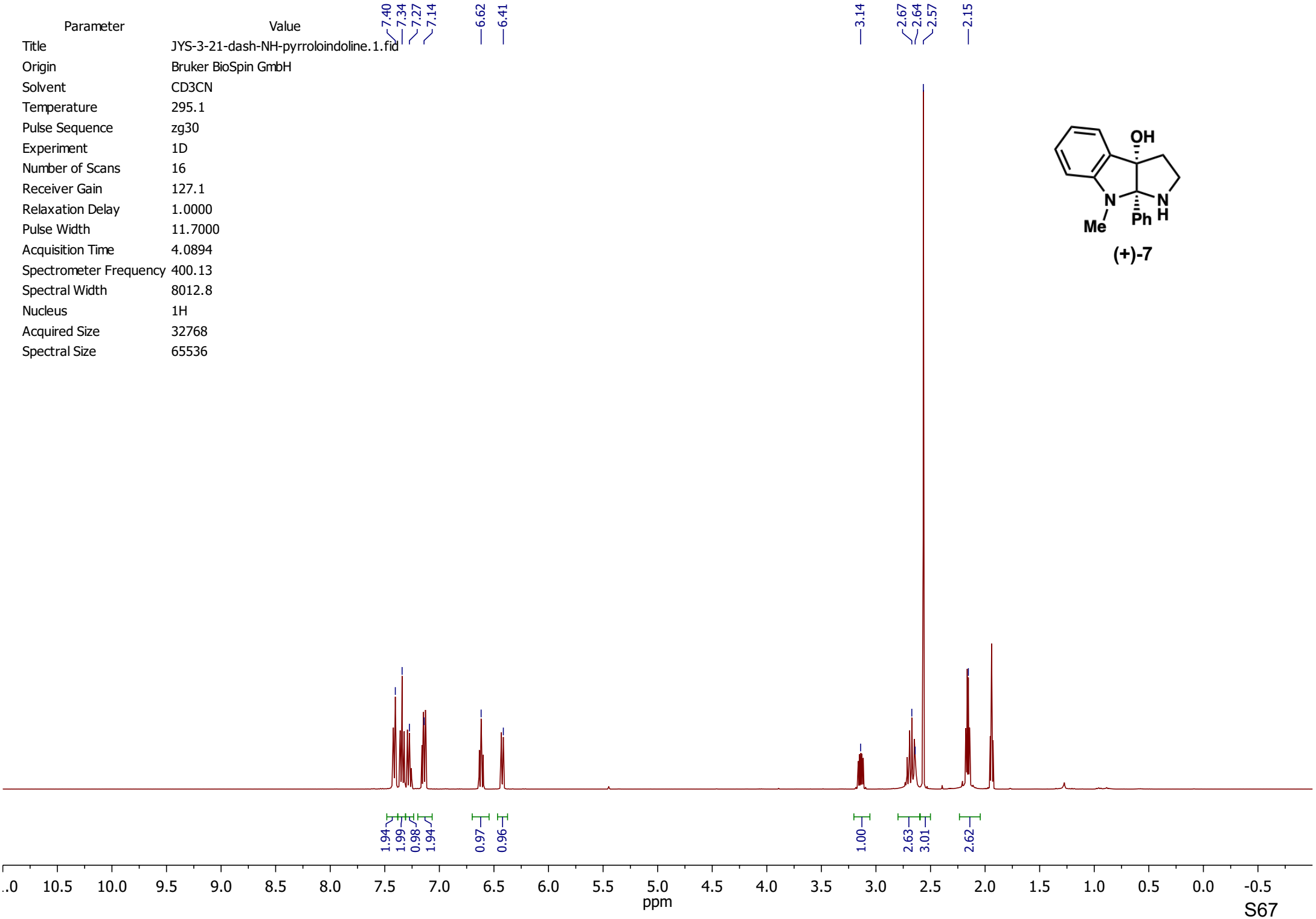
Parameter	Value
Title	CARBON01
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	512
Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	4.6125
Acquisition Time	1.0420
Acquisition Date	2018-09-19T22:55:06
Spectrometer Frequency	125.64
Spectral Width	31446.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



Parameter	Value
Title	JYS-3-21-dash-NH-pyrroloindoline.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CD3CN
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	127.1
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



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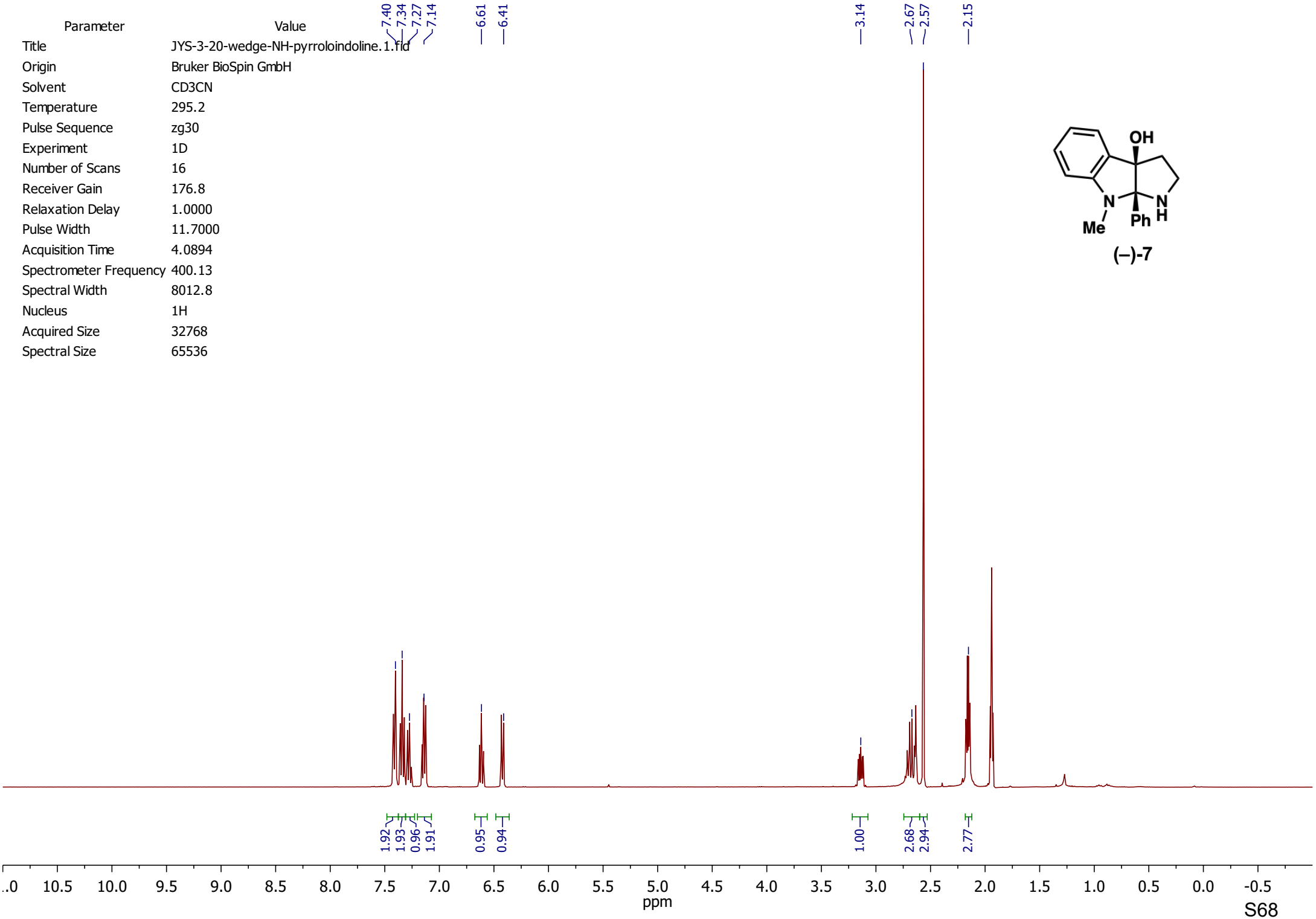
Parameter	Value
Title	JYS-3-20-wedge-NH-pyrroloindoline.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CD3CN
Temperature	295.2
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	176.8
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



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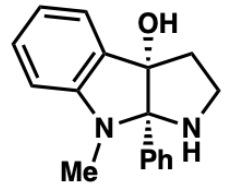
Parameter	Value
Title	JYS-3-21-dash-NH-pyrroloindoline.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CD3CN
Temperature	295.2
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	512
Receiver Gain	55.5
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



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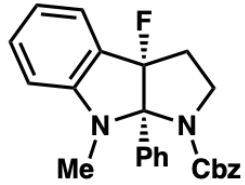
Parameter	Value
Title	JYS-2-300-F1-3F-Cbz-dash.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	127.1
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



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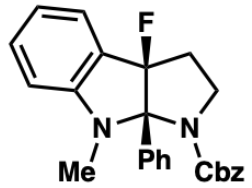
Parameter	Value
Title	JYS-2-298-F1-3F-Cbz-wedge.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	127.1
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



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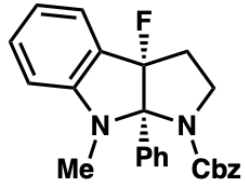
Parameter	Value
Title	JYS-2-300-F1-3F-Cbz-dash.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	512
Receiver Gain	72.0
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



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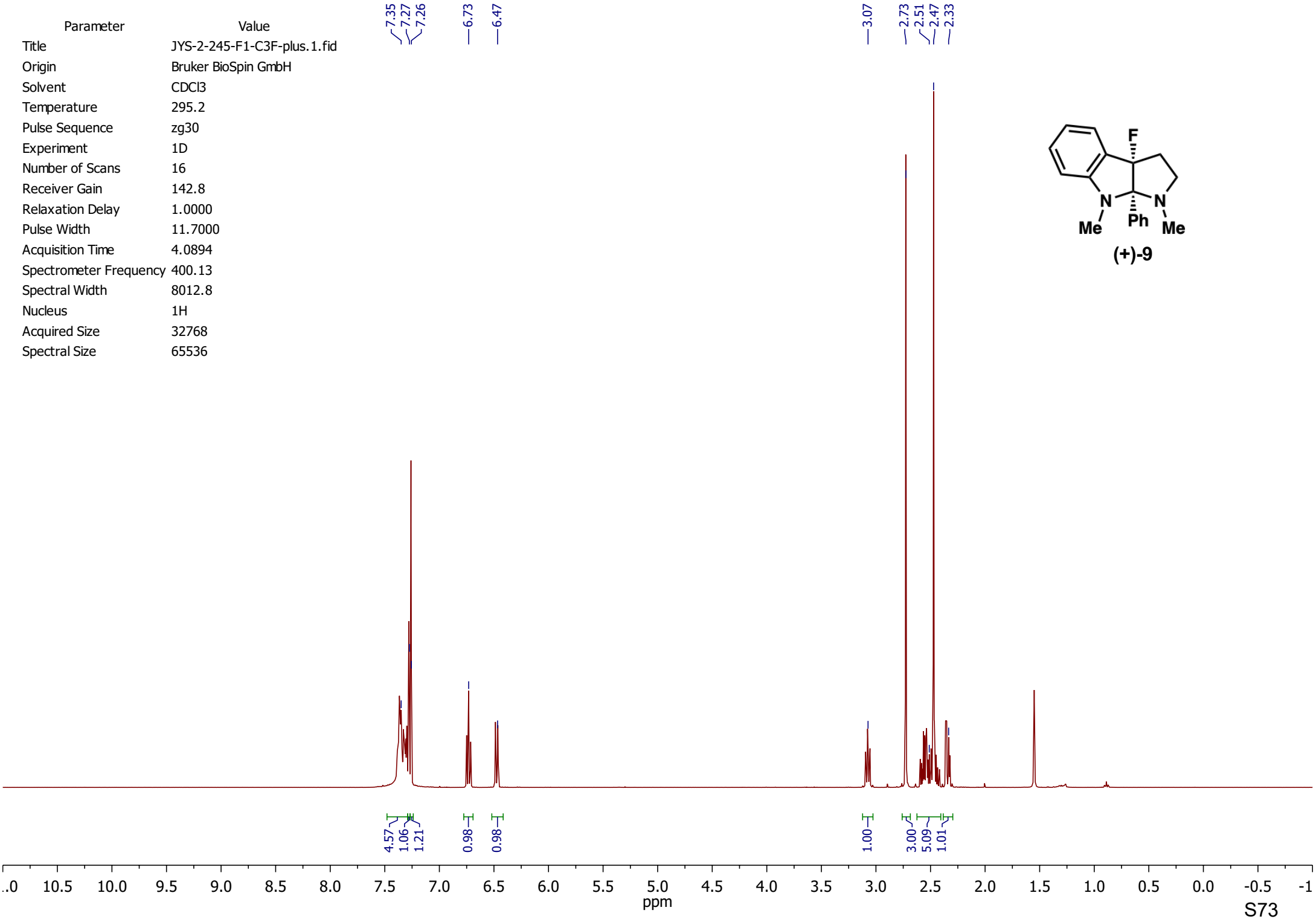
Parameter	Value
Title	JYS-2-245-F1-C3F-plus.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	142.8
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



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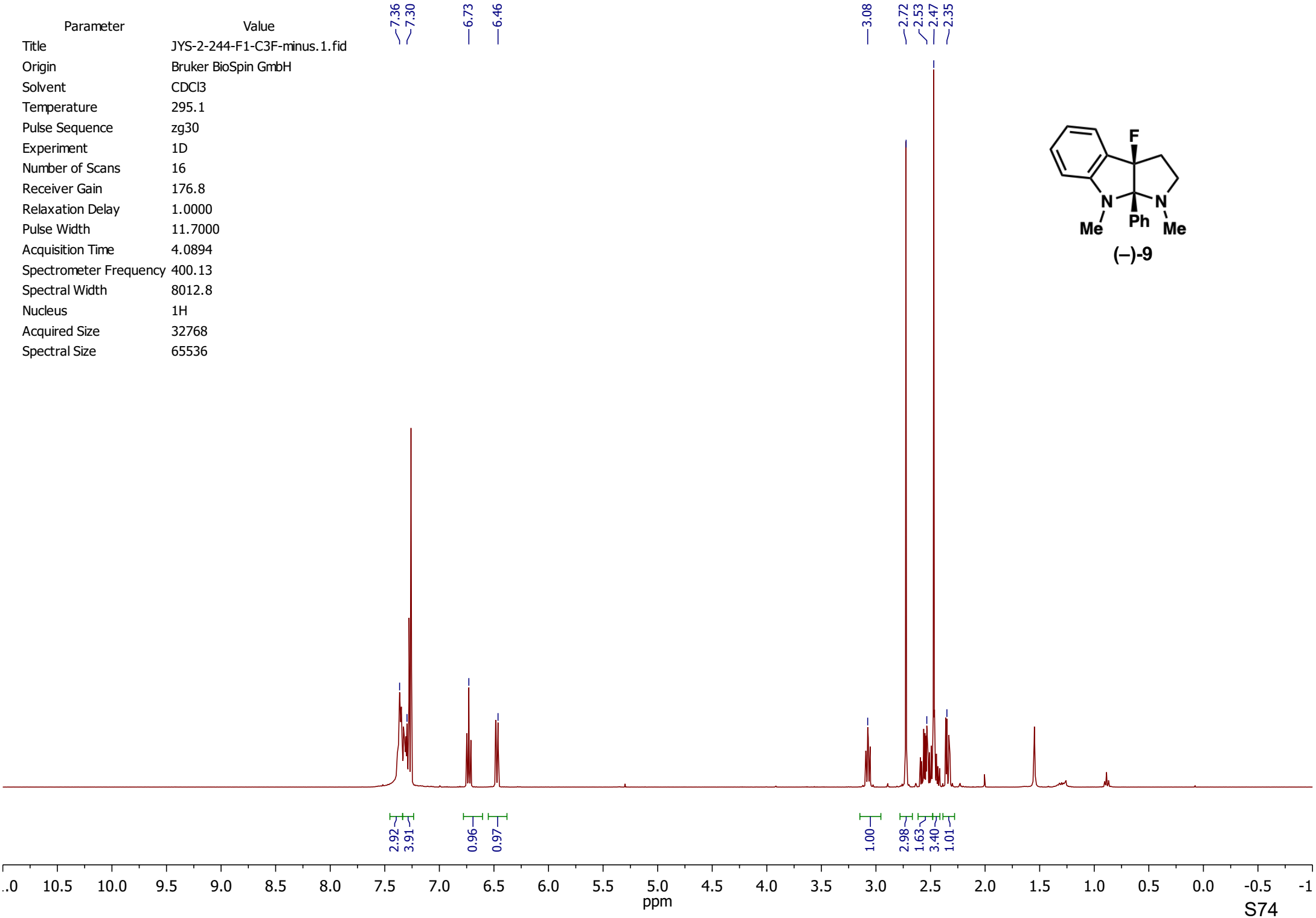
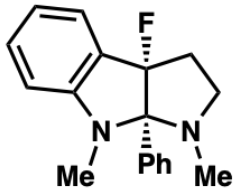
Parameter	Value
Title	JYS-2-244-F1-C3F-minus.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	176.8
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



Parameter	Value
Title	JYS-2-245-F1-C3F-plus.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	512
Receiver Gain	72.0
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



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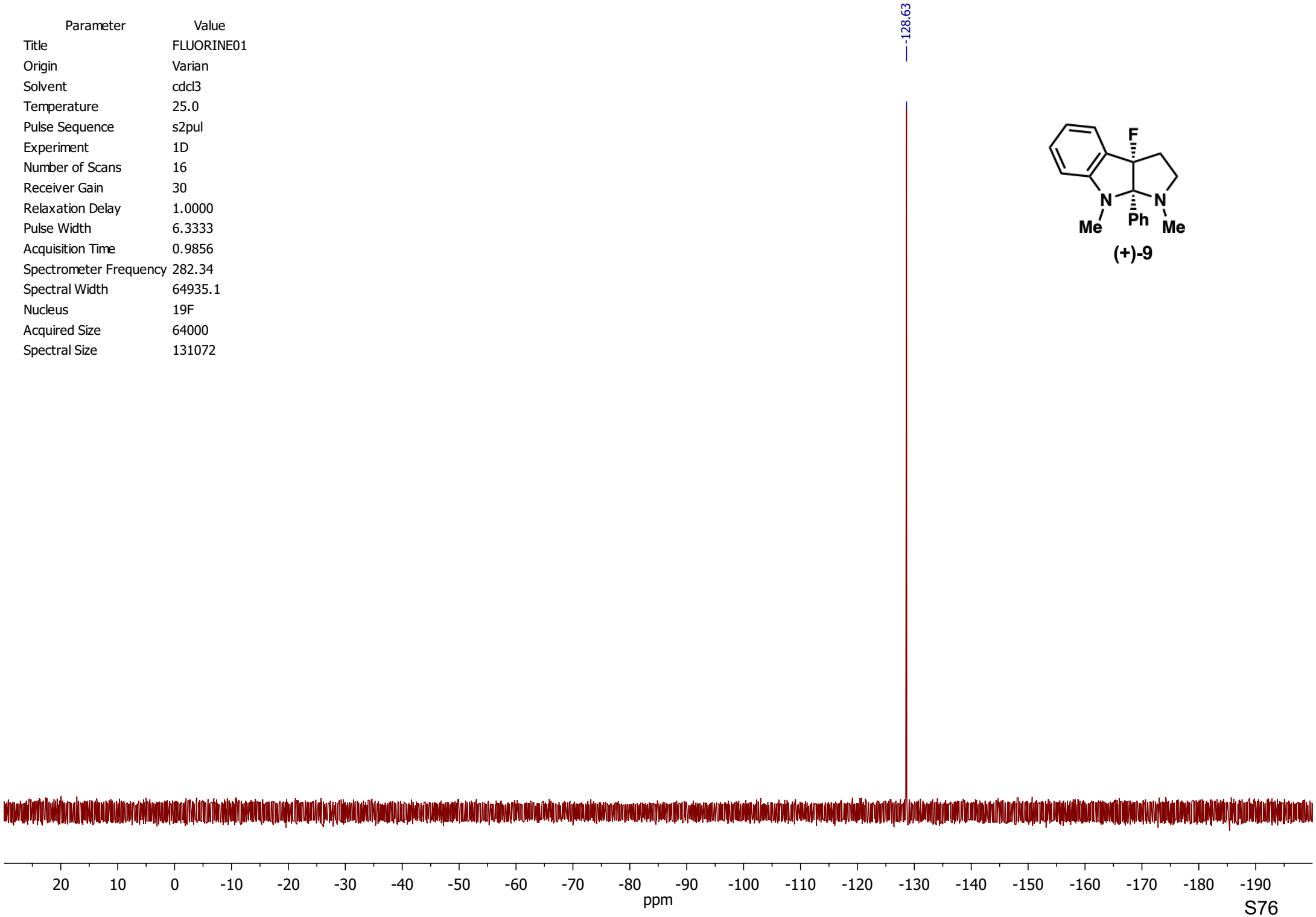
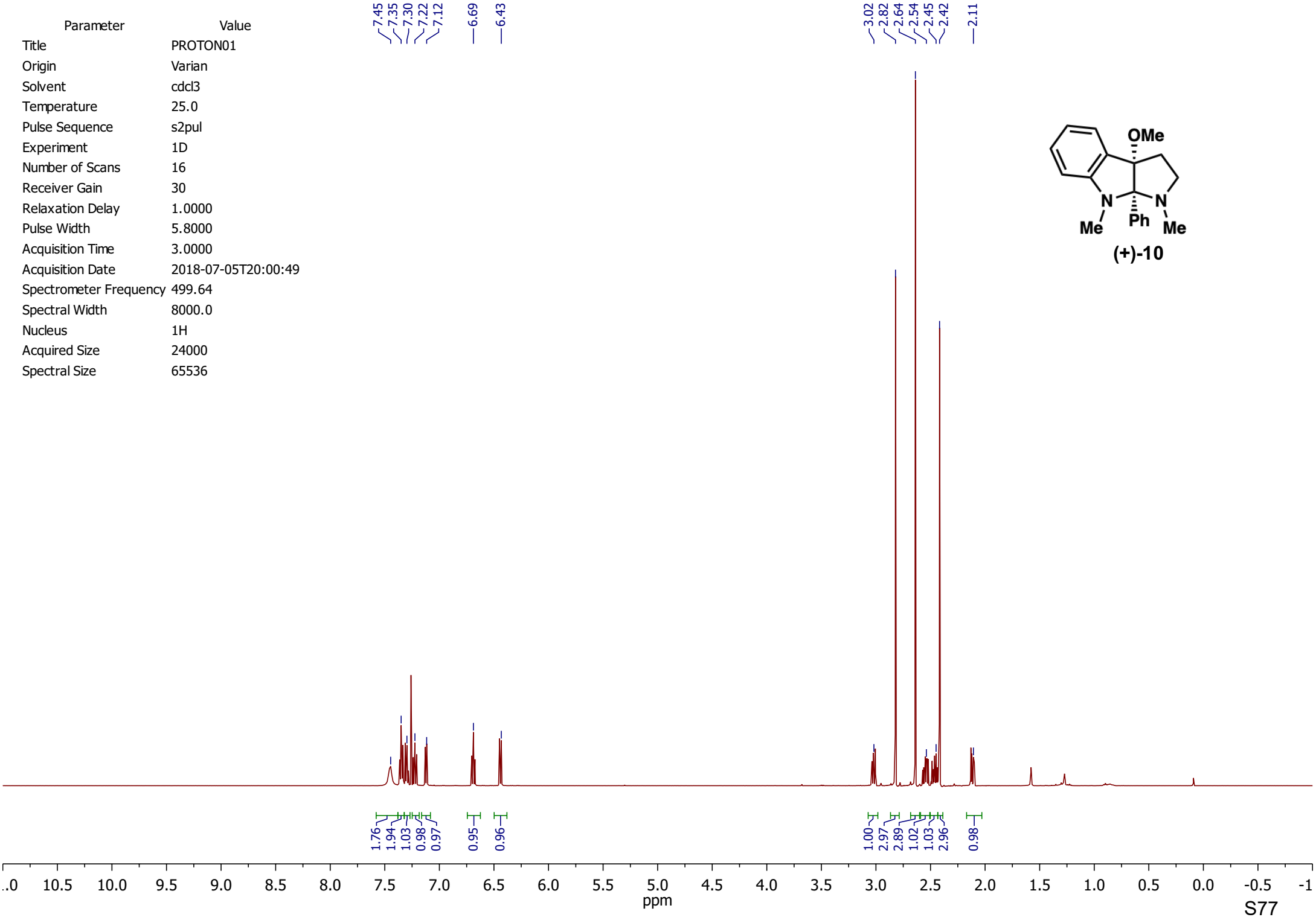
Parameter	Value
Title	FLUORINE01
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	6.3333
Acquisition Time	0.9856
Spectrometer Frequency	282.34
Spectral Width	64935.1
Nucleus	19F
Acquired Size	64000
Spectral Size	131072



Parameter	Value
Title	PROTON01
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	5.8000
Acquisition Time	3.0000
Acquisition Date	2018-07-05T20:00:49
Spectrometer Frequency	499.64
Spectral Width	8000.0
Nucleus	1H
Acquired Size	24000
Spectral Size	65536



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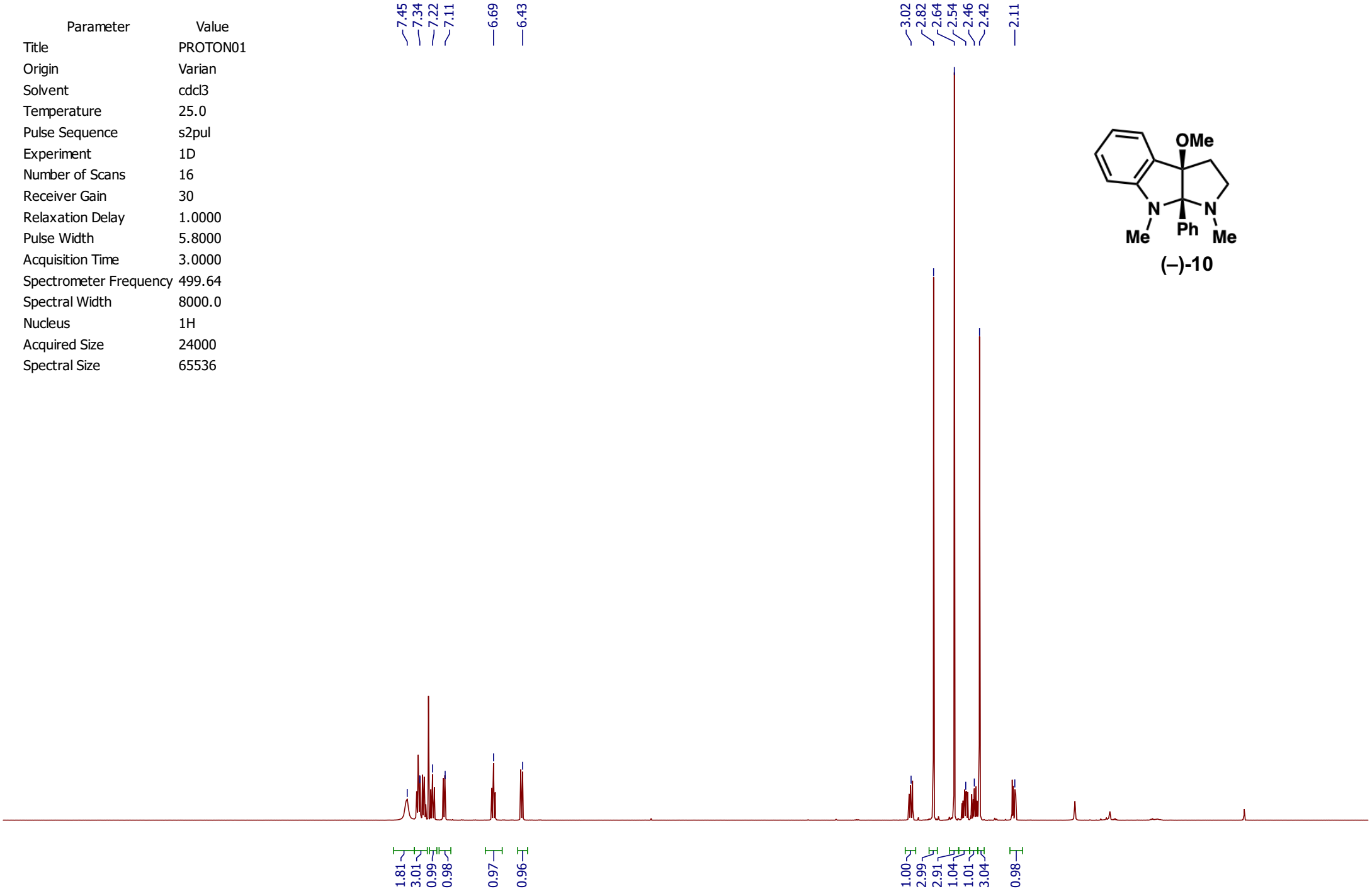
Parameter	Value
Title	PROTON01
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	5.8000
Acquisition Time	3.0000
Spectrometer Frequency	499.64
Spectral Width	8000.0
Nucleus	1H
Acquired Size	24000
Spectral Size	65536



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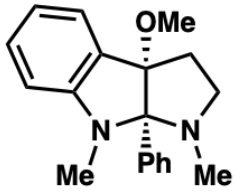
Parameter	Value
Title	CARBON01
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	512
Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	4.6125
Acquisition Time	1.0420
Acquisition Date	2018-07-05T20:32:56
Spectrometer Frequency	125.65
Spectral Width	31446.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



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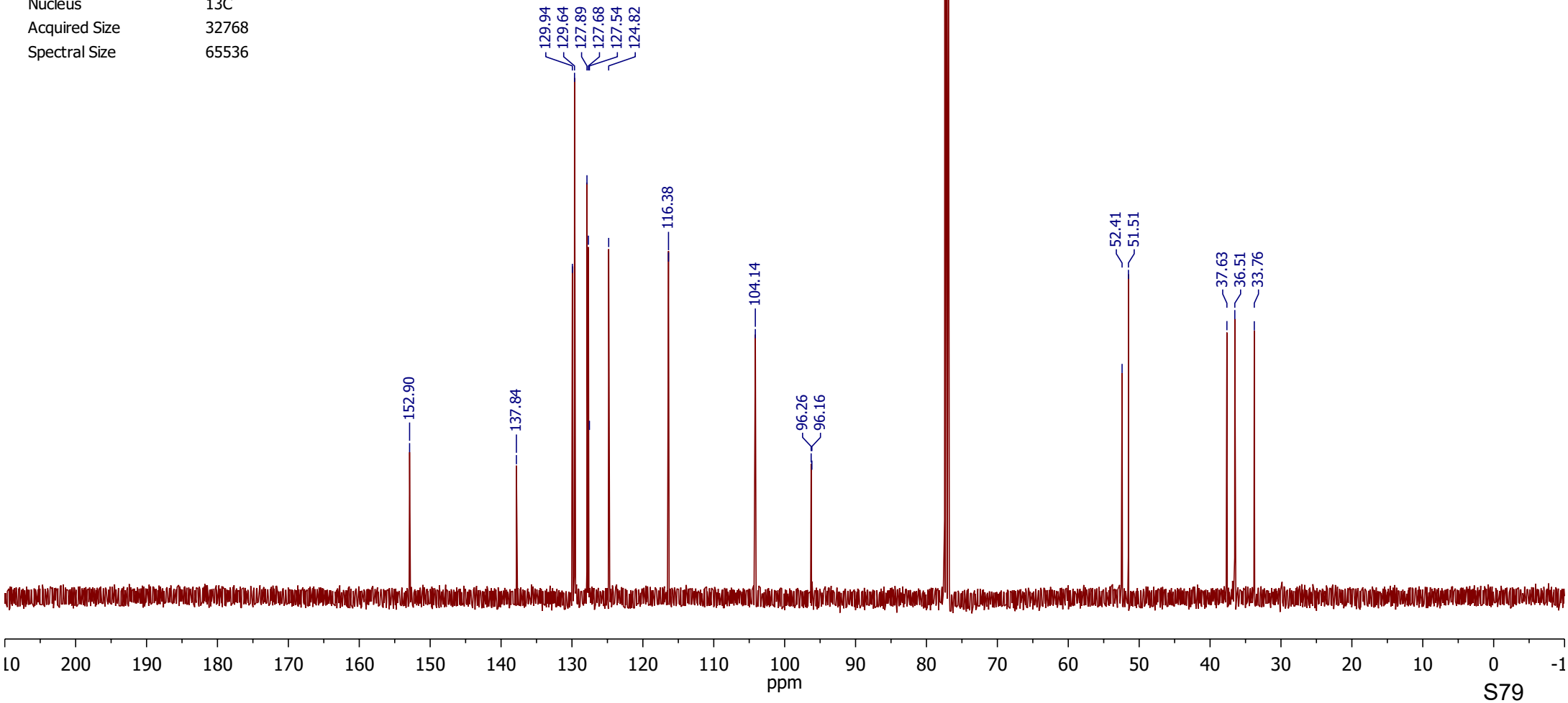
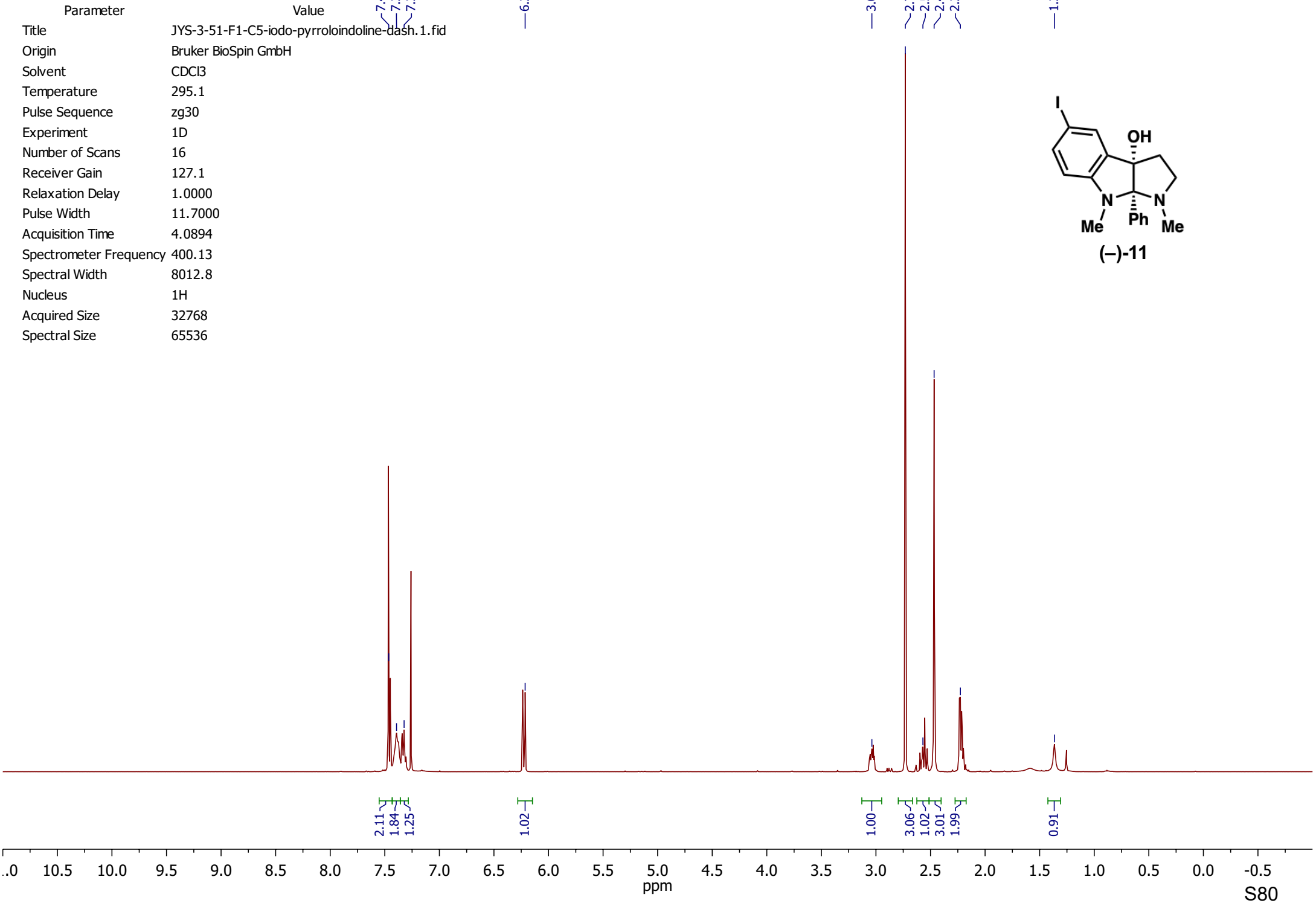
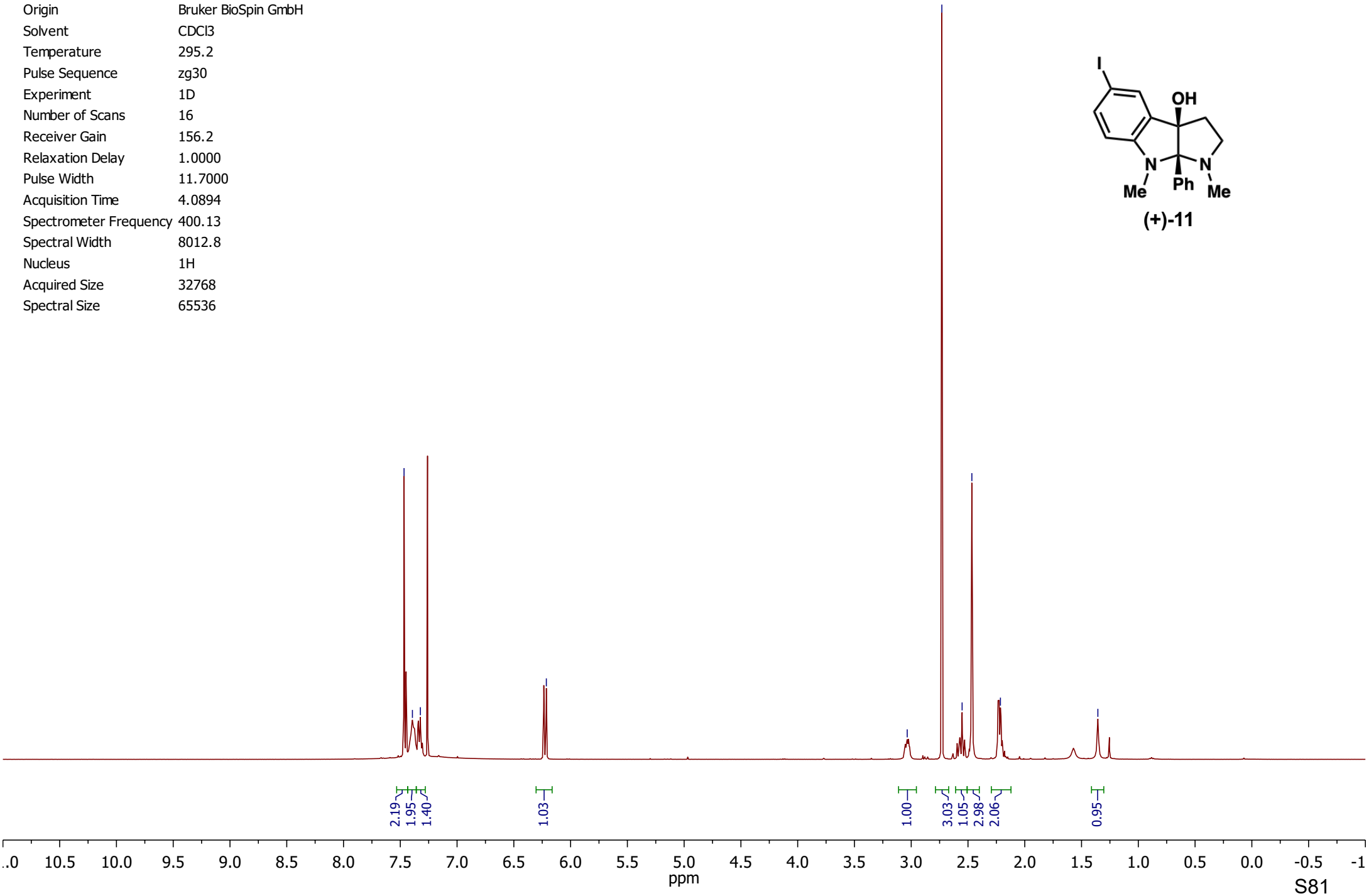


Parameter	Value
Title	JYS-3-51-F1-C5-iodo-pyrroloindoline-dash.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	127.1
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



Parameter	Value
Title	JYS-3-50-F1-C5-iodo-pyrroloindoline-wedge.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	156.2
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



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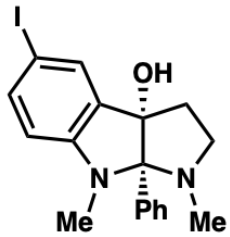
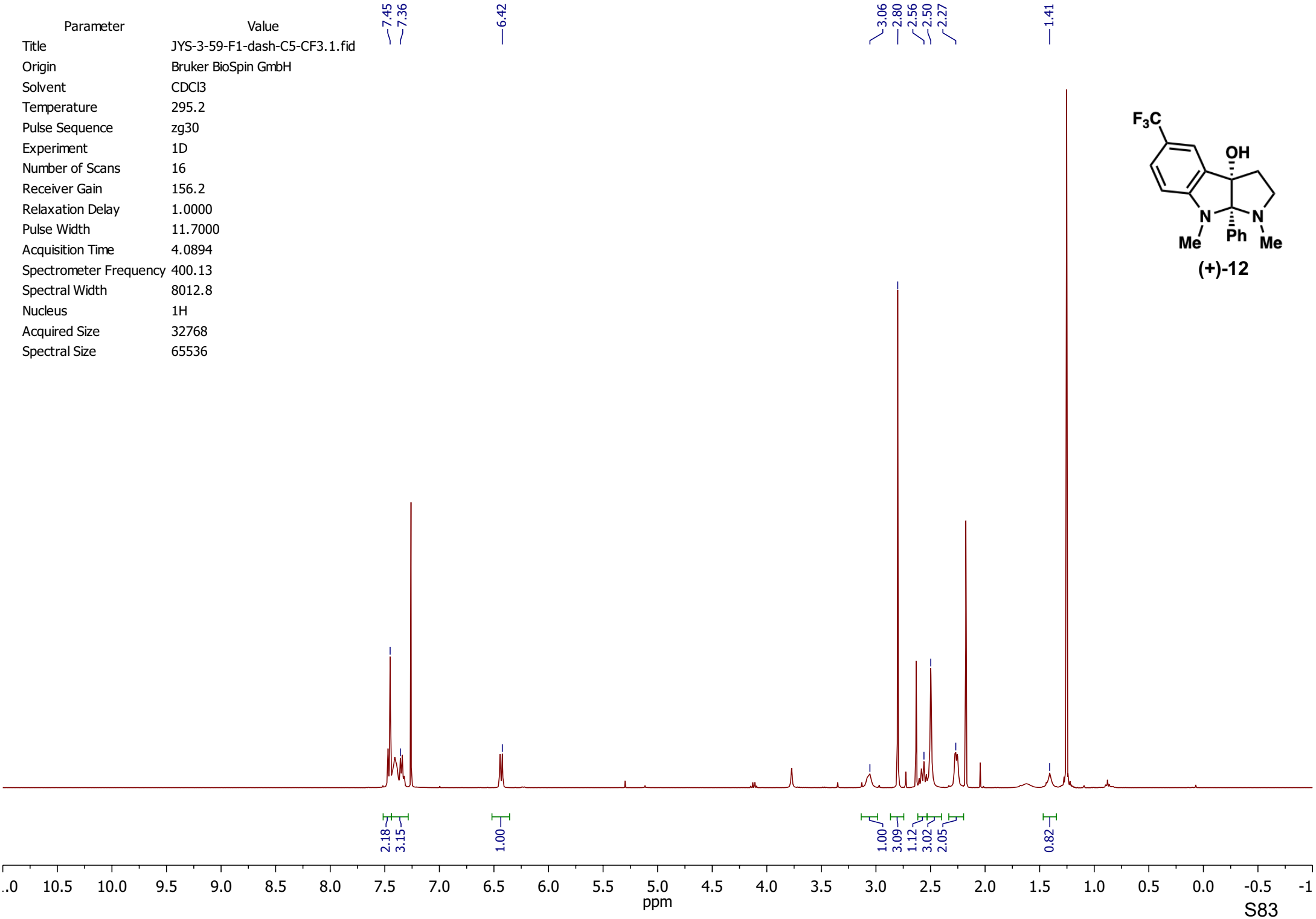
Parameter	Value
Title	JYS-3-51-F1-C5-iodo-pyrroloindoline-dash.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	512
Receiver Gain	78.7
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



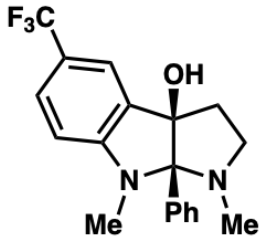
(–)-11

Parameter	Value
Title	JYS-3-59-F1-dash-C5-CF3.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	156.2
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



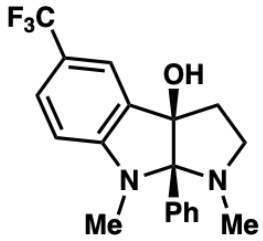
(+)-12

Parameter	Value
Title	JYS-3-58-F1-wedge-C5-CF3.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	156.2
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



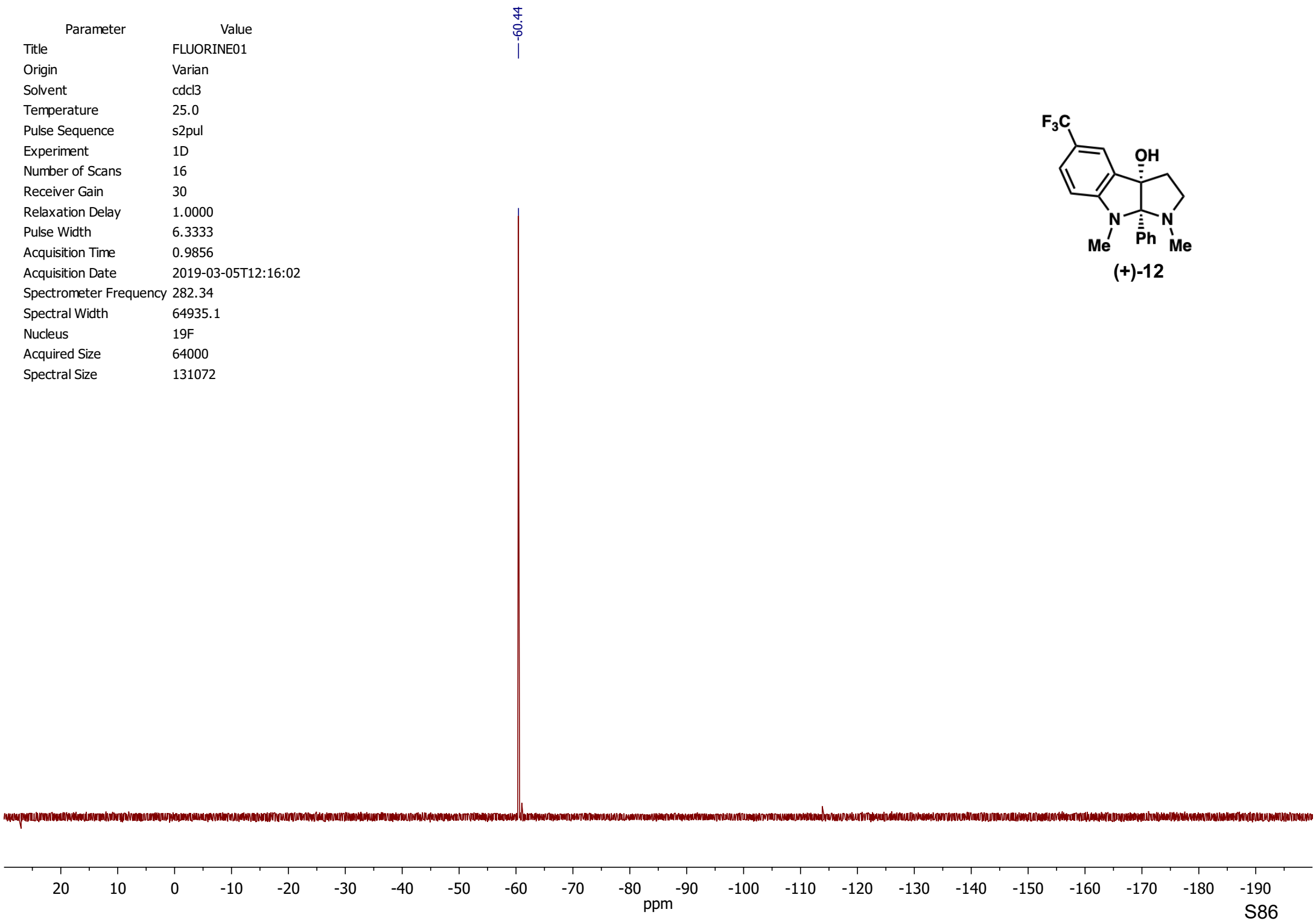
(–)-12

Parameter	Value
Title	JYS-3-58-F1-wedge-C5-CF3.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	512
Receiver Gain	55.5
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



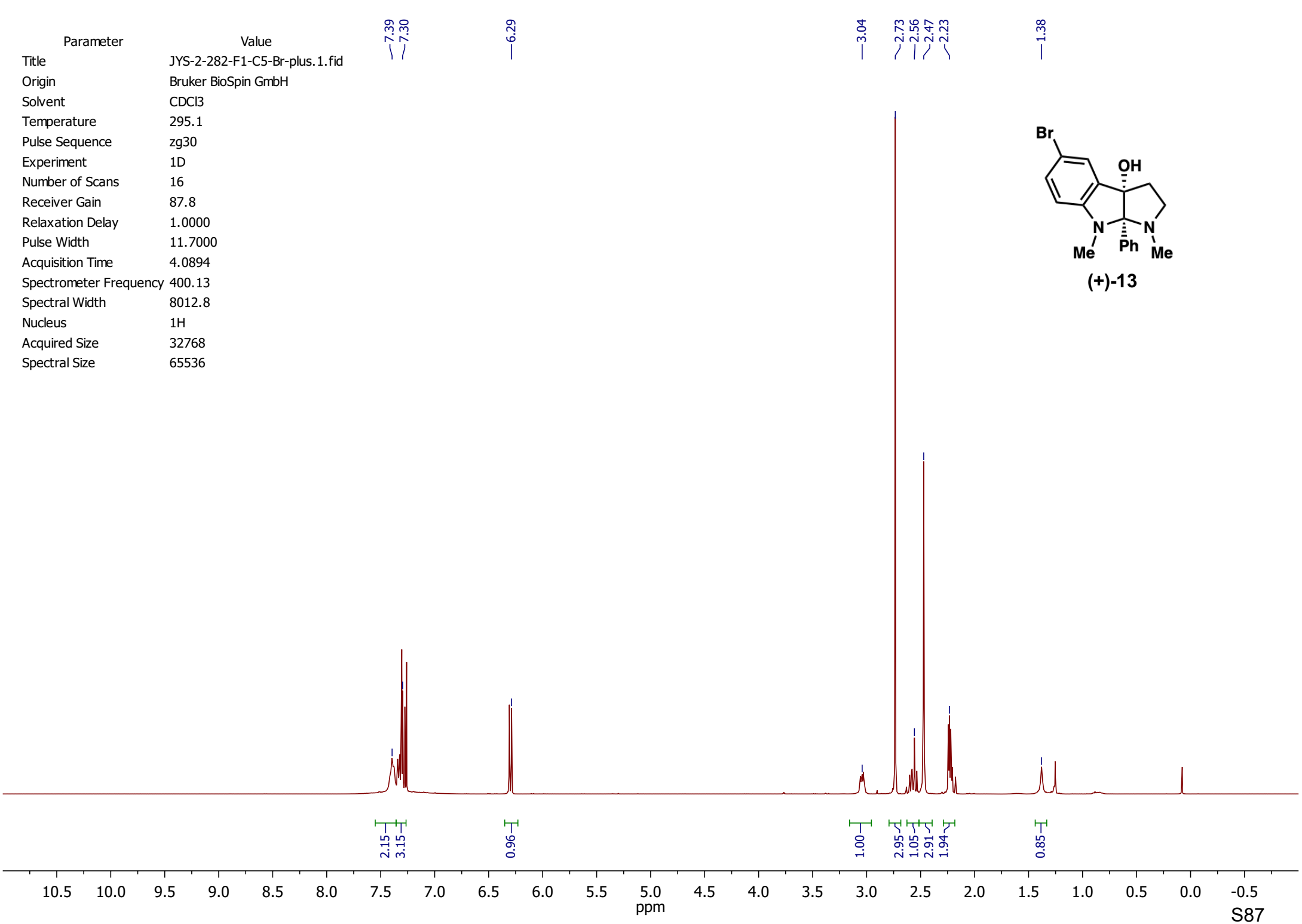
(–)-12

Parameter	Value
Title	FLUORINE01
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Experiment	1D
Number of Scans	16
Receiver Gain	30
Relaxation Delay	1.0000
Pulse Width	6.3333
Acquisition Time	0.9856
Acquisition Date	2019-03-05T12:16:02
Spectrometer Frequency	282.34
Spectral Width	64935.1
Nucleus	19F
Acquired Size	64000
Spectral Size	131072

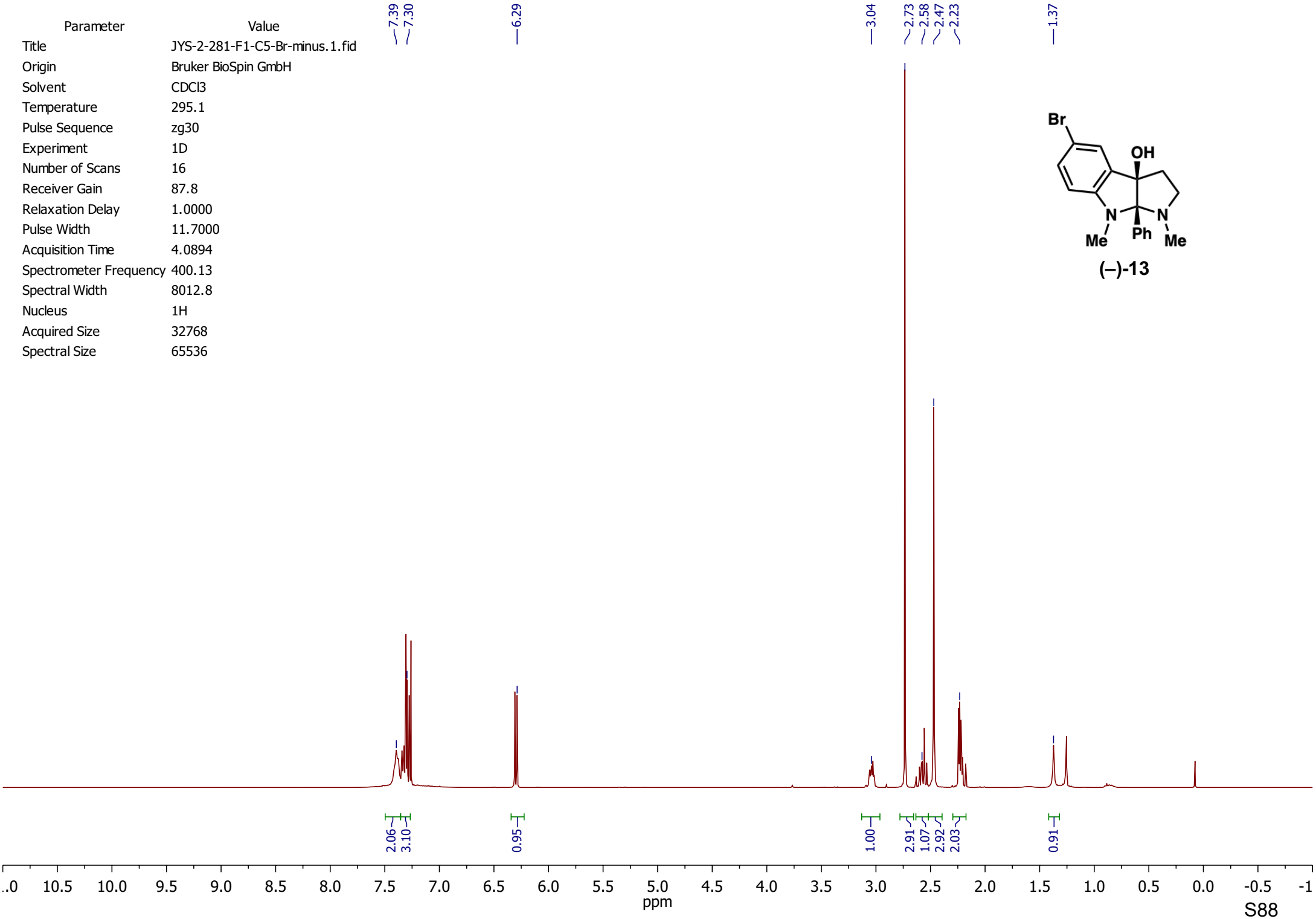


(+)-12

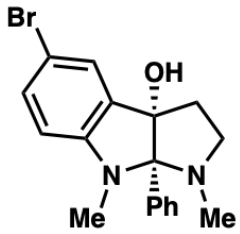
Parameter	Value
Title	JYS-2-282-F1-C5-Br-plus.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	87.8
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



Parameter	Value
Title	JYS-2-281-F1-C5-Br-minus.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	87.8
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

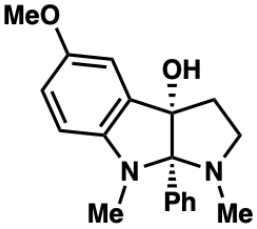


Parameter	Value
Title	JYS-2-282-F1-C5-Br-plus.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	384
Receiver Gain	55.5
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



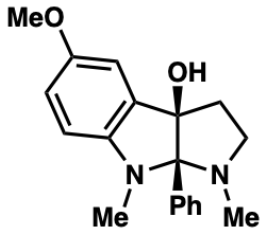
(+)-13

Parameter	Value
Title	JYS-2-285-F1-second-C5-OMe-plus.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	112.8
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



(+)-14

Parameter	Value
Title	JYS-2-284-F1-second-C5-OMe-minus.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	127.1
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



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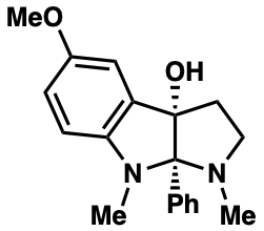
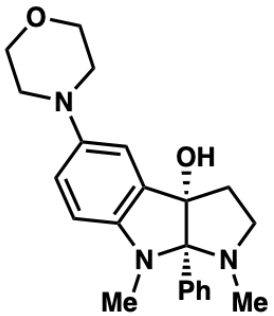
Parameter	Value
Title	JYS-2-285-F1-second-C5-OMe-plus.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	128
Receiver Gain	50.3
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



(+)-14

Parameter	Value
Title	JYS-2-287-F1-C5-morpholino.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.2
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	142.8
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



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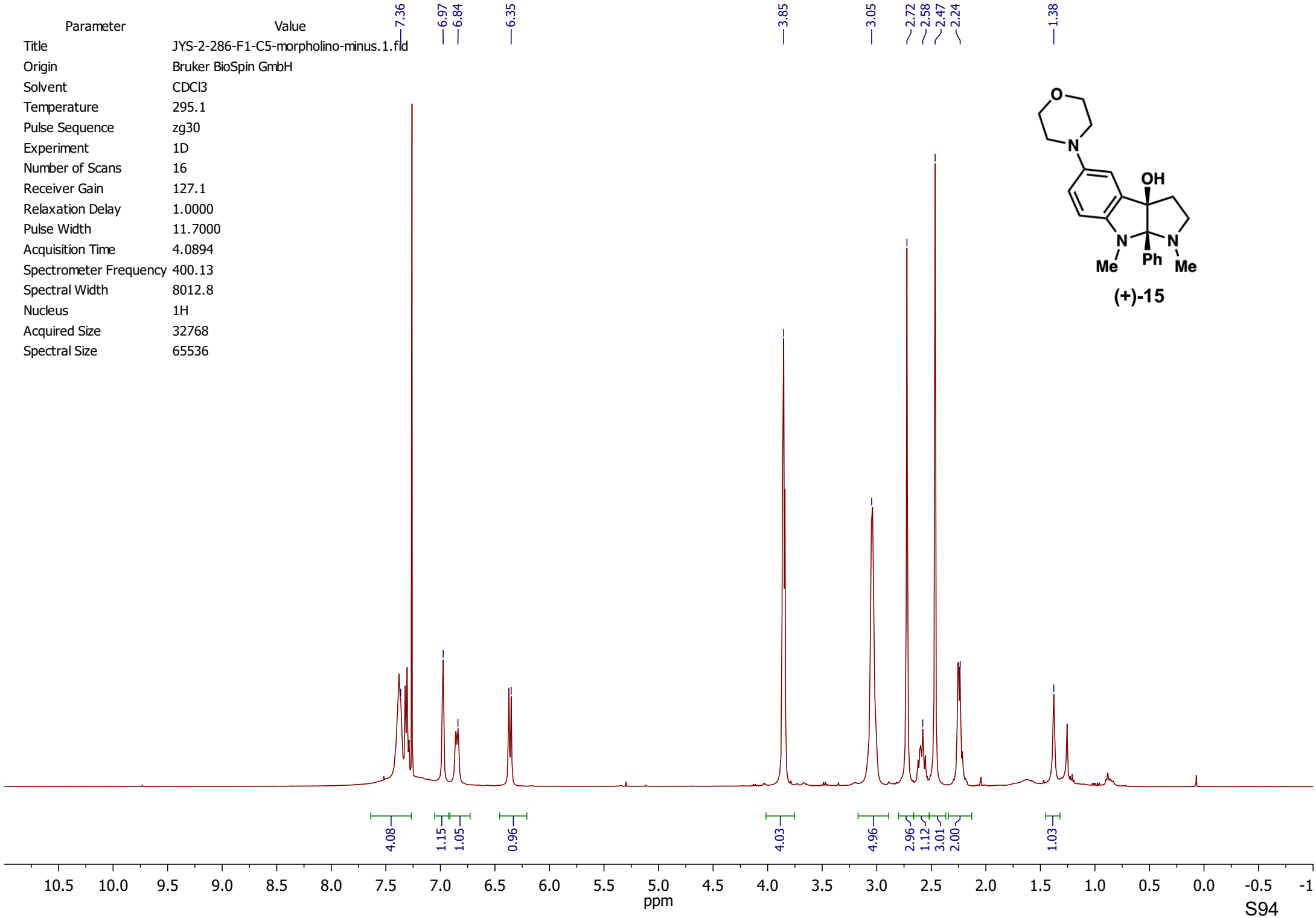
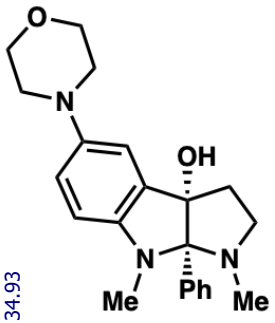
Parameter	Value
Title	JYS-2-286-F1-C5-morpholino-minus.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	127.1
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



Parameter	Value
Title	JYS-2-287-F1-C5-morpholino.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	512
Receiver Gain	87.8
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

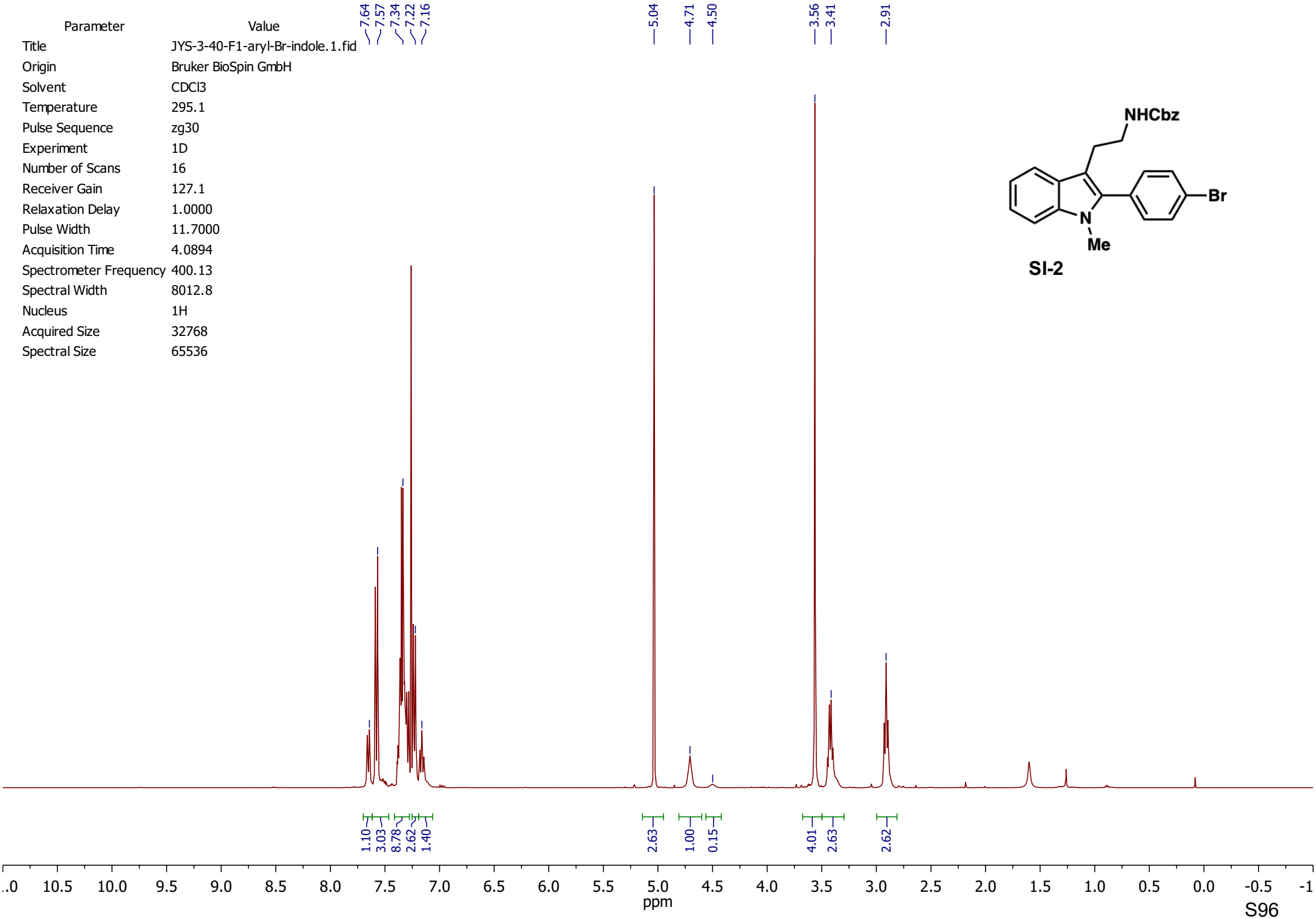


(–)-15

147.78
143.69
137.46
131.92
128.92
128.16
118.70
114.48
104.35
98.85
90.97
67.33
51.84
51.65
40.70
36.72
34.93

ppm

Parameter	Value
Title	JYS-3-40-F1-aryl-Br-indole.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	127.1
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



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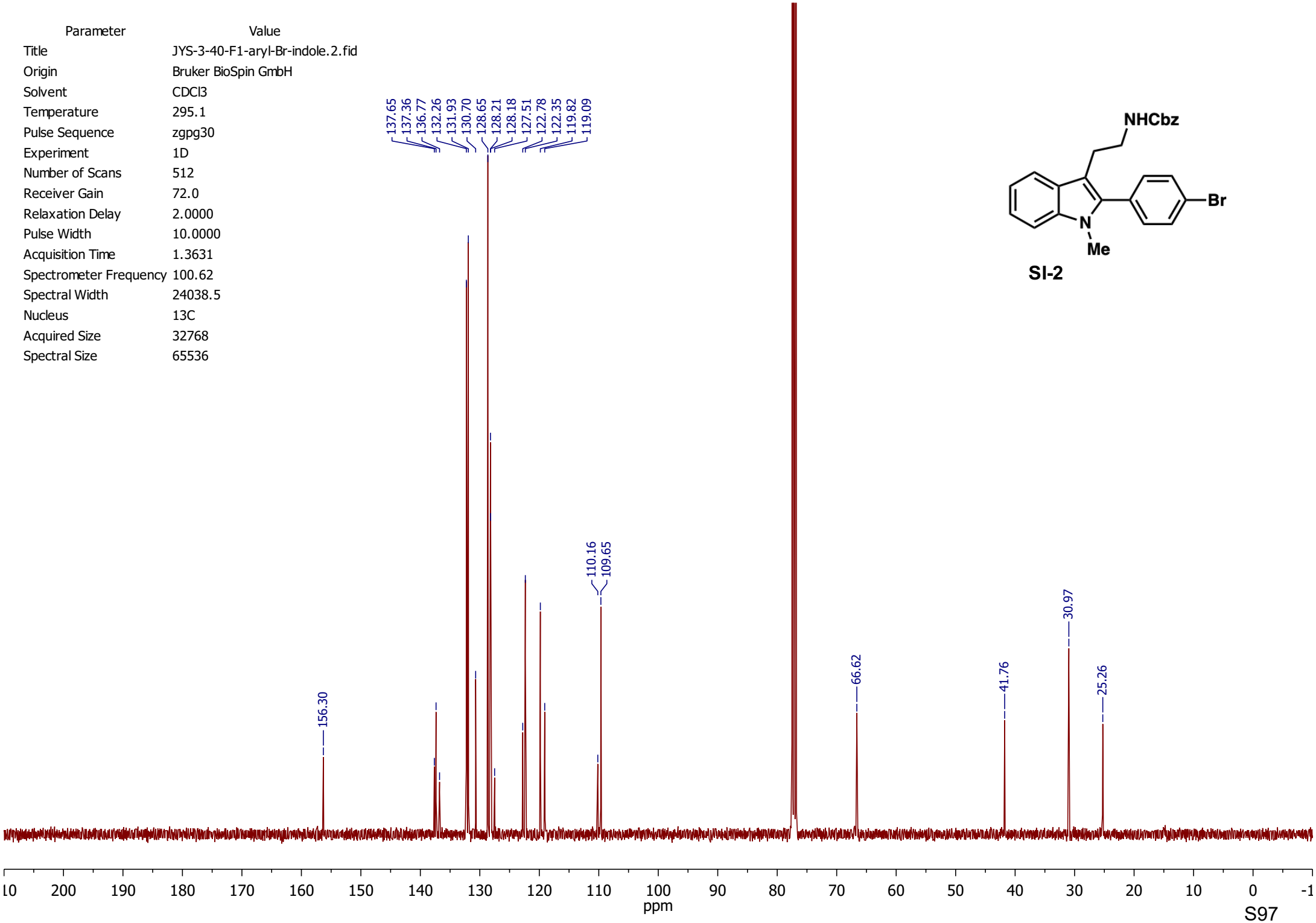
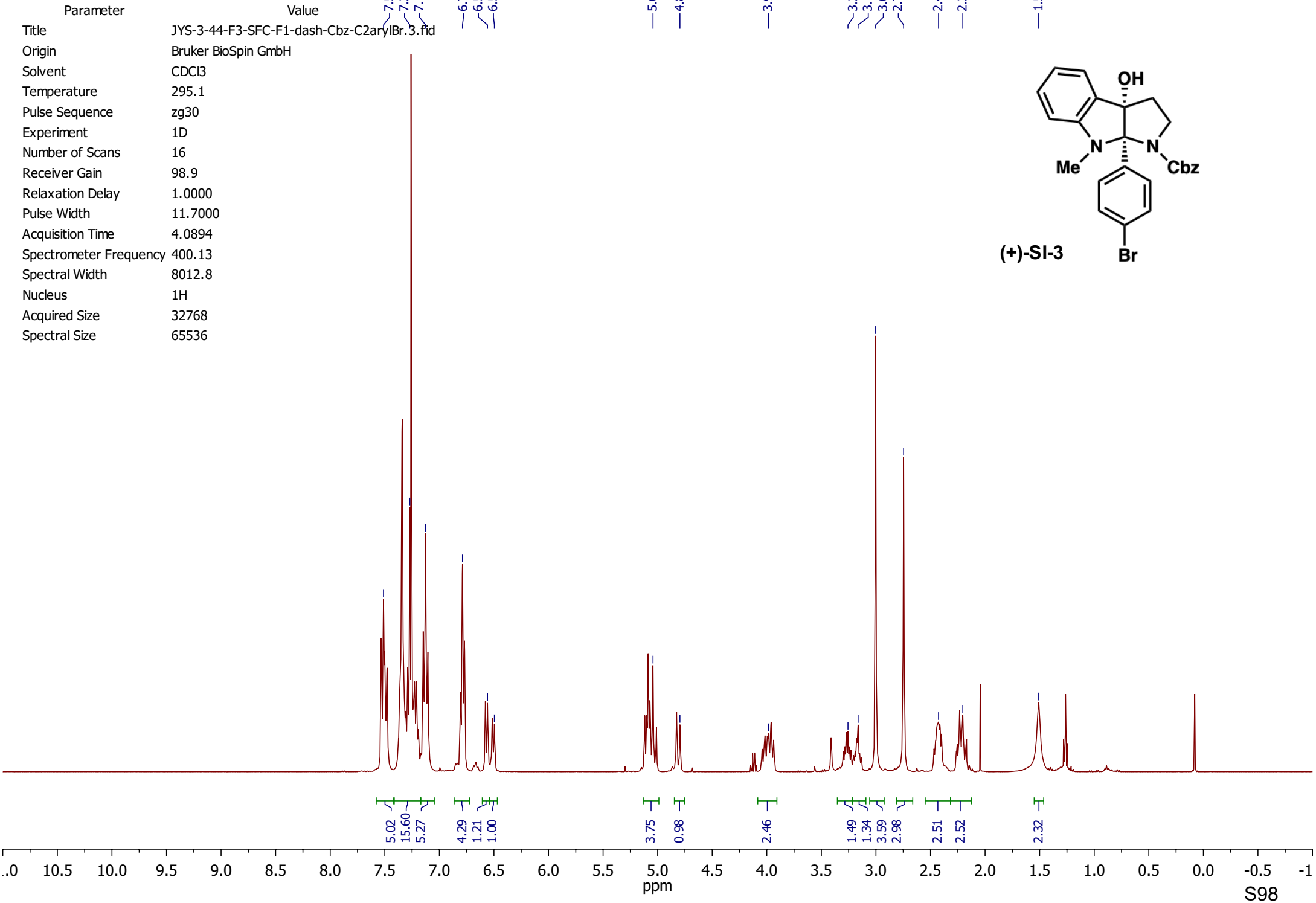
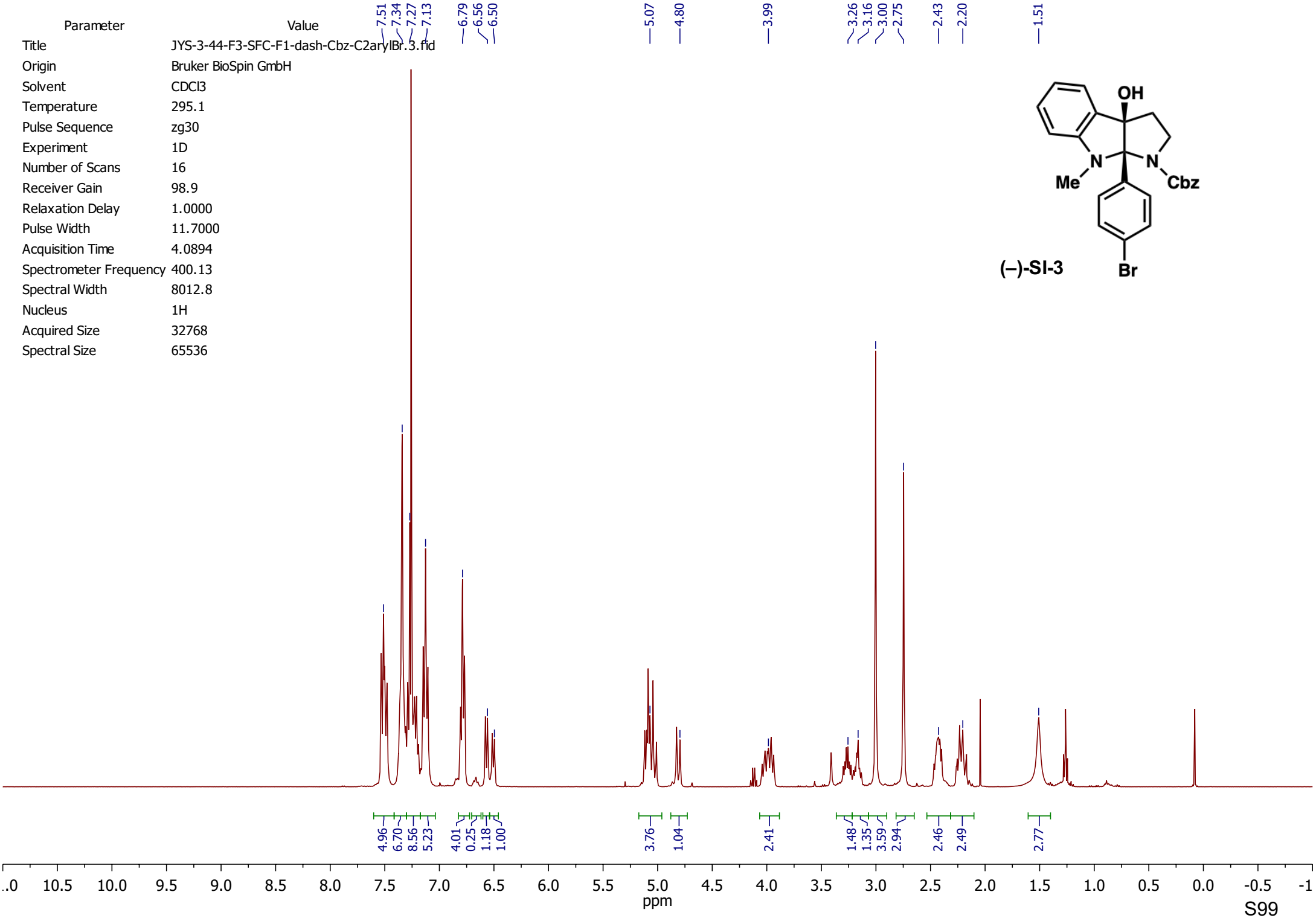
Parameter	Value
Title	JYS-3-40-F1-aryl-Br-indole.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	512
Receiver Gain	72.0
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



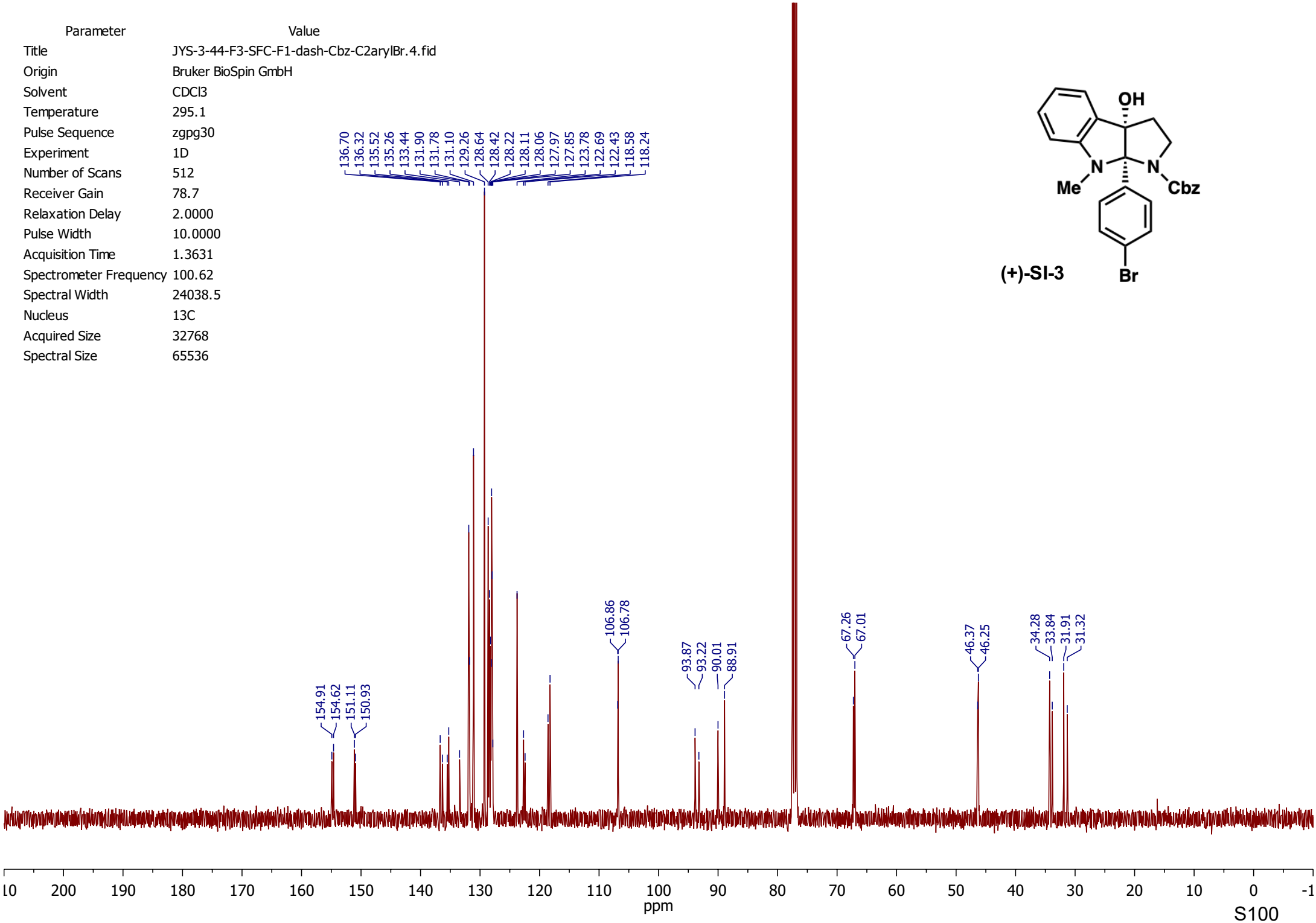
Parameter	Value
Title	JYS-3-44-F3-SFC-F1-dash-Cbz-C2arylBr.3.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	98.9
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



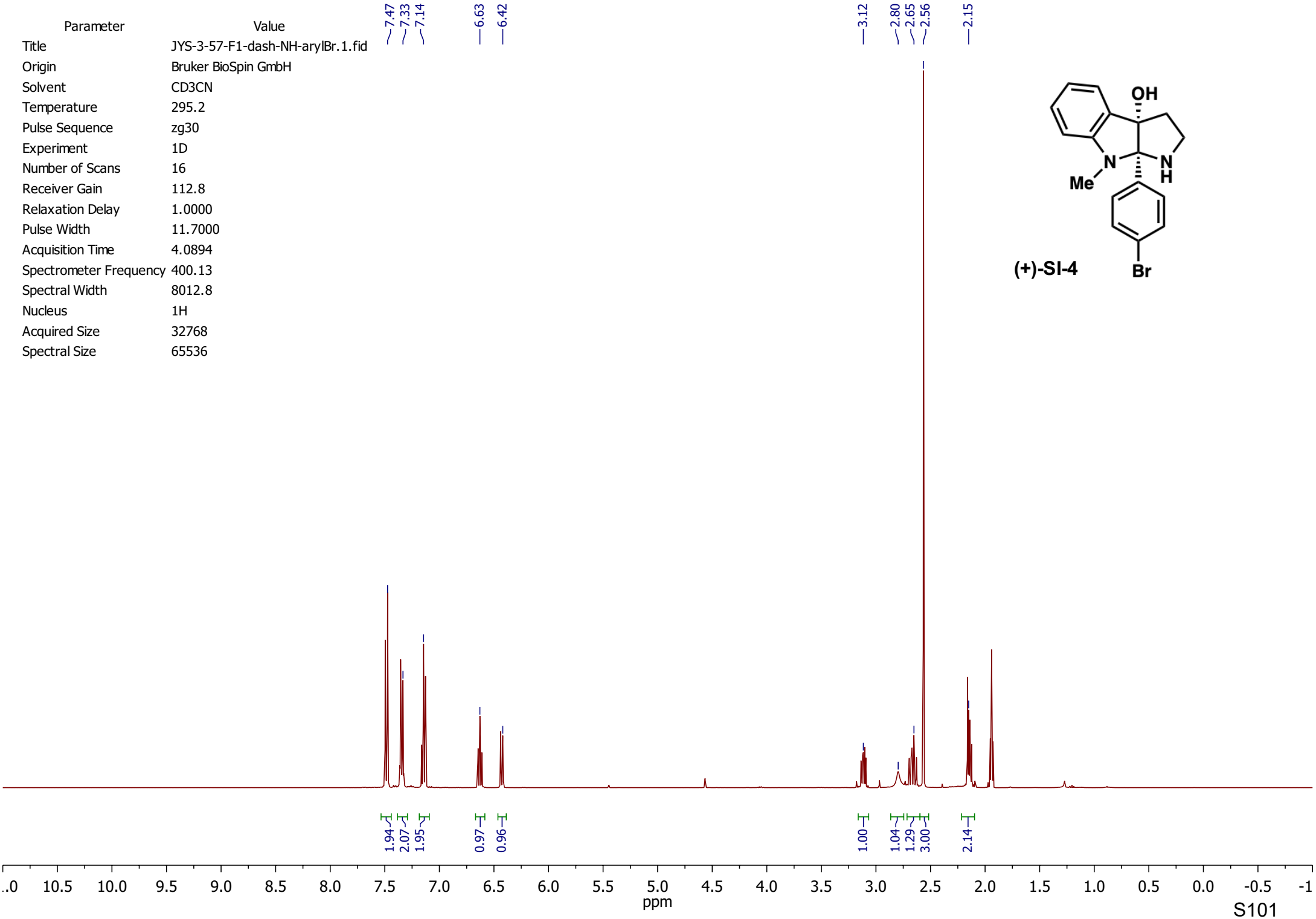
Parameter	Value
Title	JYS-3-44-F3-SFC-F1-dash-Cbz-C2arylBr.3.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	98.9
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



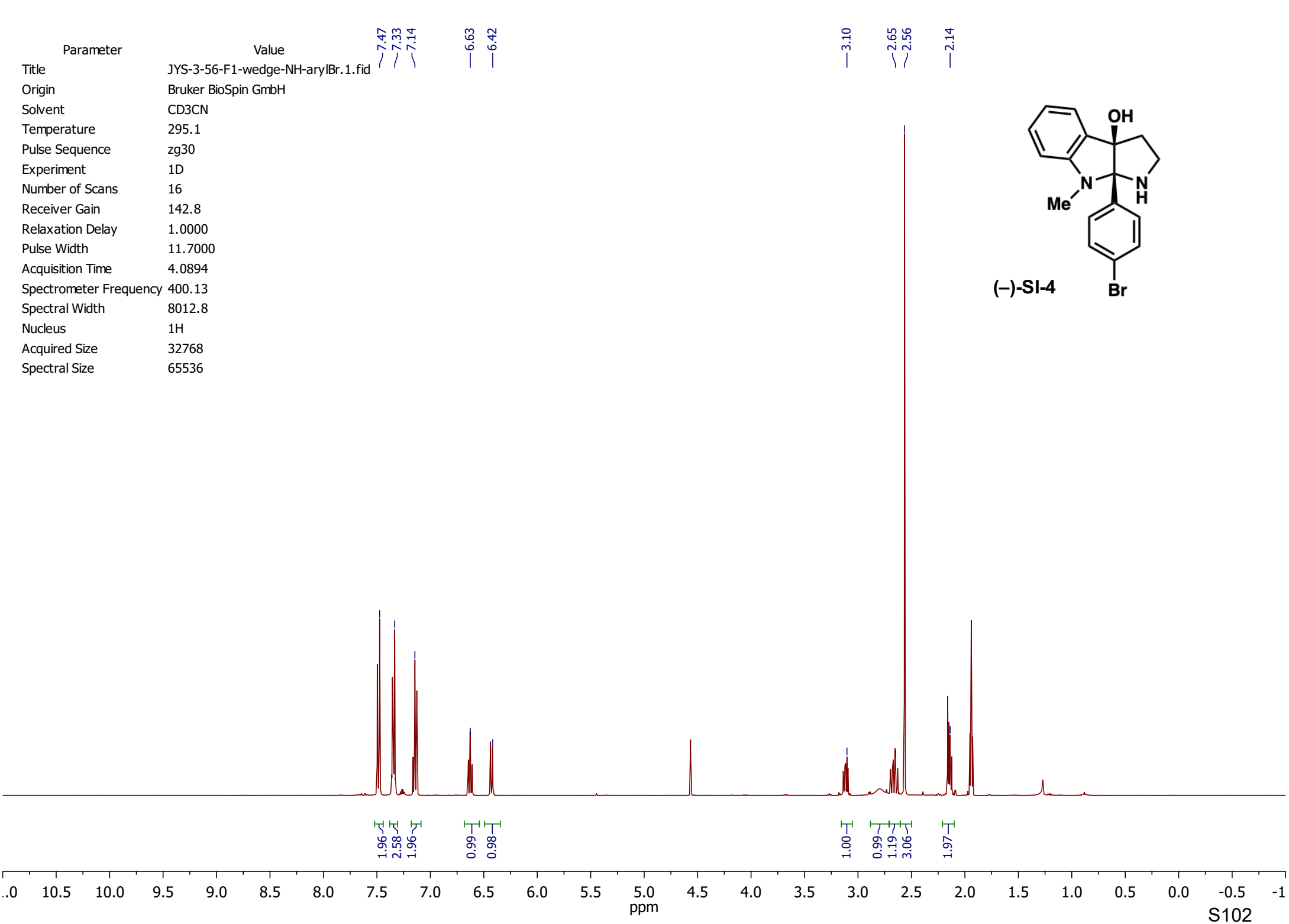
Parameter	Value
Title	JYS-3-44-F3-SFC-F1-dash-Cbz-C2arylBr.4.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	512
Receiver Gain	78.7
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



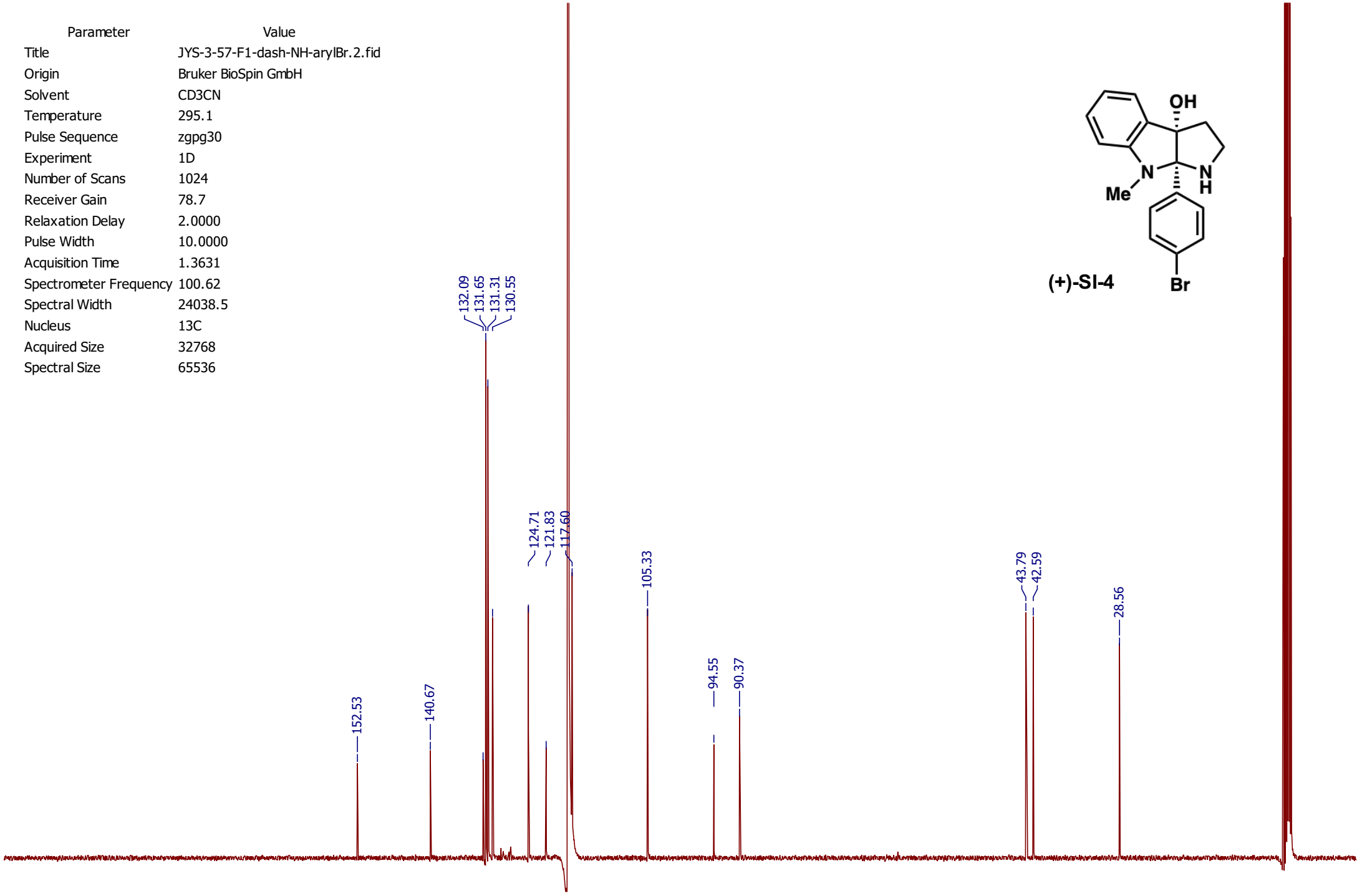
Parameter	Value
Title	JYS-3-57-F1-dash-NH-arylBr.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CD3CN
Temperature	295.2
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	112.8
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



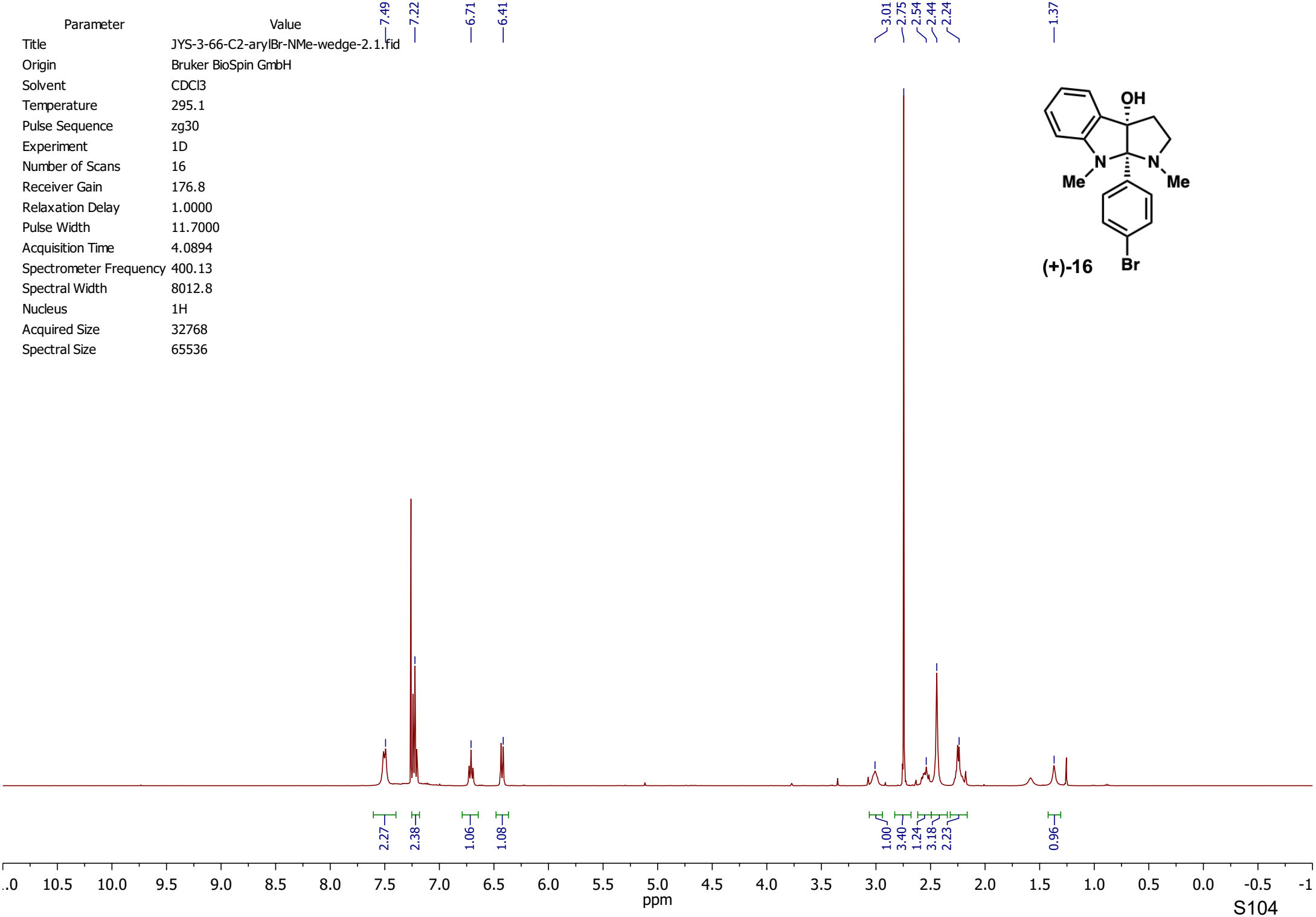
Parameter	Value
Title	JYS-3-56-F1-wedge-NH-arylBr.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CD3CN
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	142.8
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



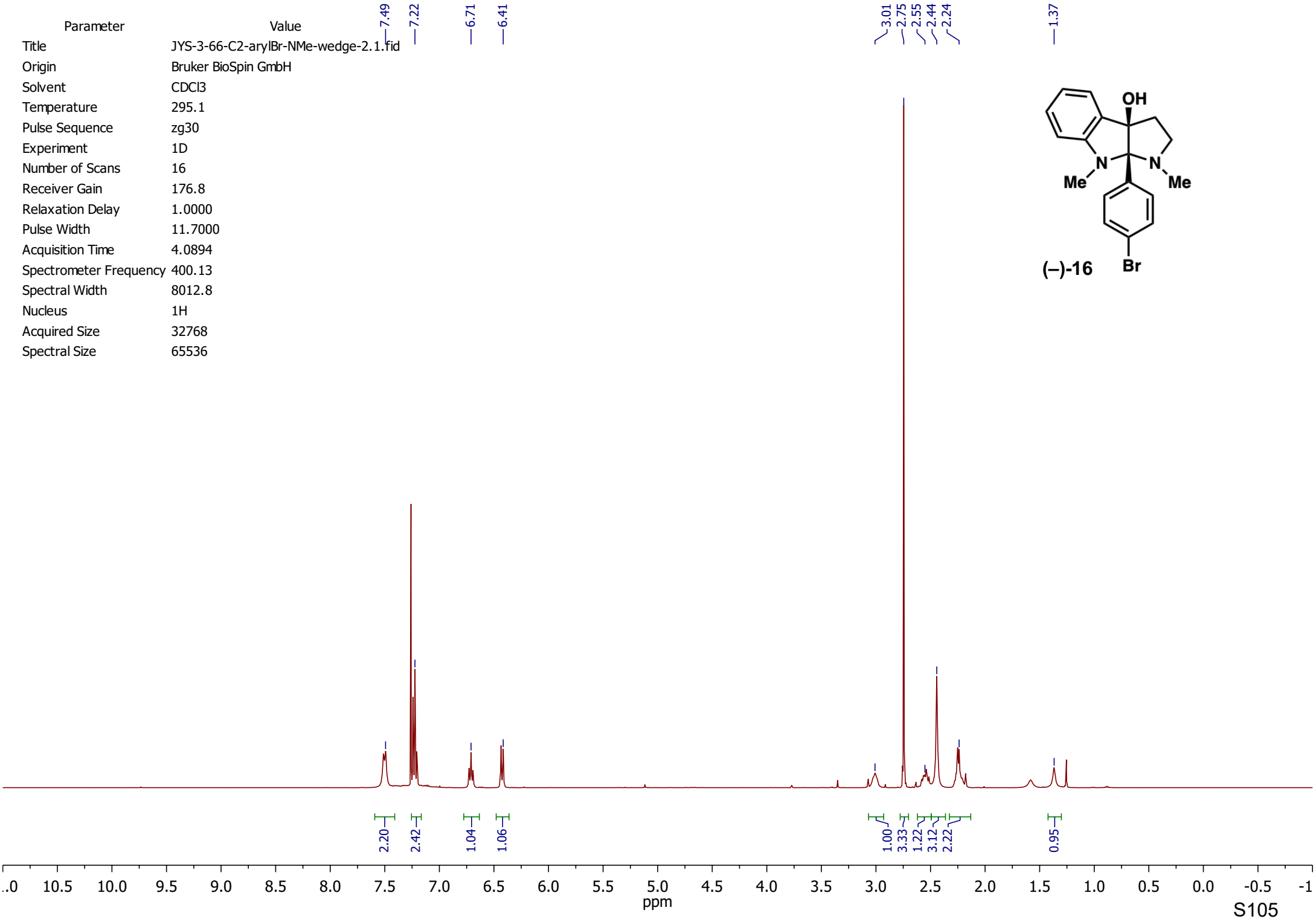
Parameter	Value
Title	JYS-3-57-F1-dash-NH-arylBr.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CD3CN
Temperature	295.1
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	1024
Receiver Gain	78.7
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



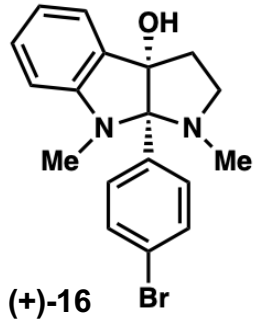
Parameter	Value
Title	JYS-3-66-C2-arylBr-NMe-wedge-2.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	176.8
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



Parameter	Value
Title	JYS-3-66-C2-arylBr-NMe-wedge-2.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	176.8
Relaxation Delay	1.0000
Pulse Width	11.7000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



Parameter	Value
Title	JYS-3-66-C2-arylBr-NMe-wedge-2.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	295.1
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	1024
Receiver Gain	87.8
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



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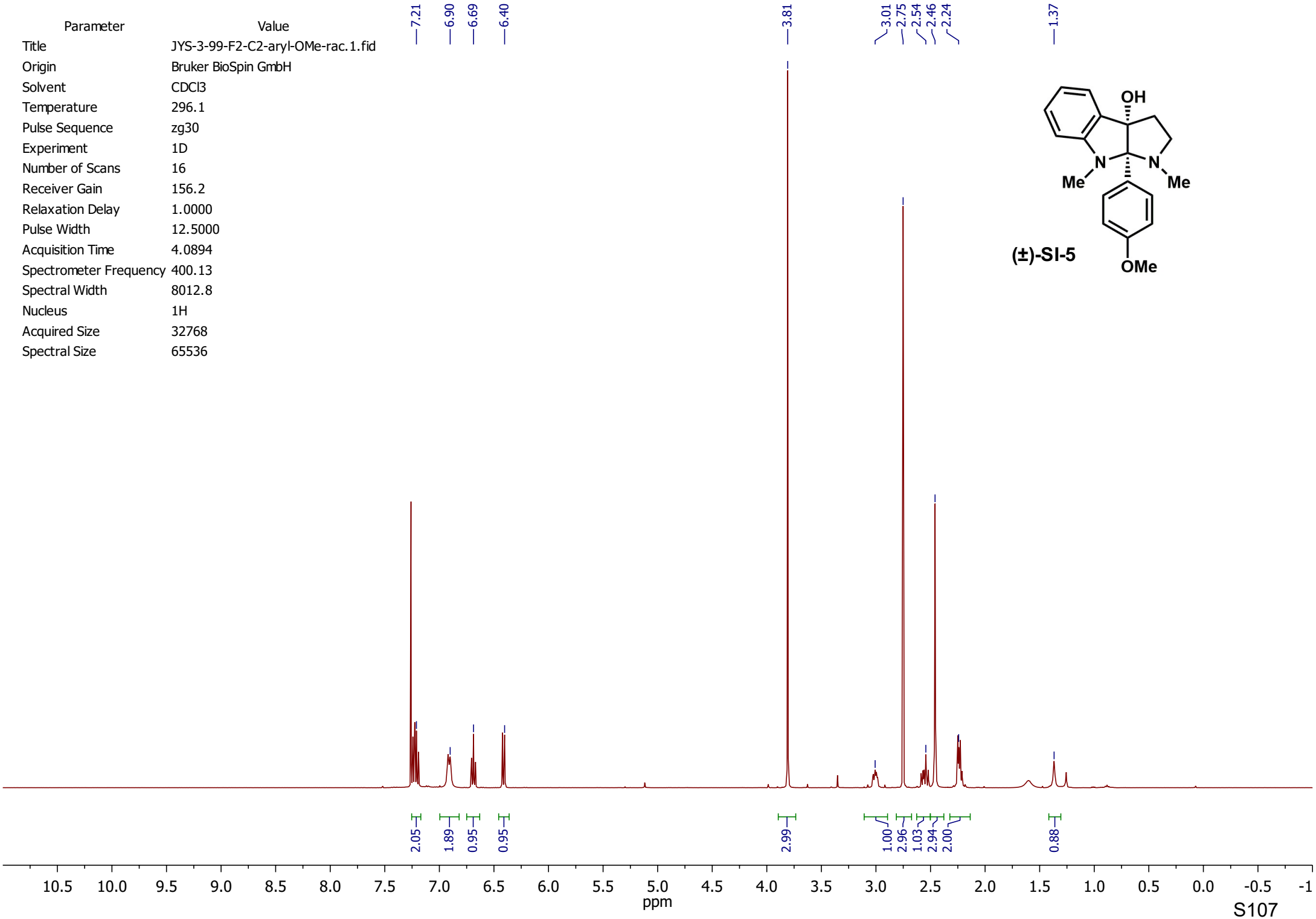
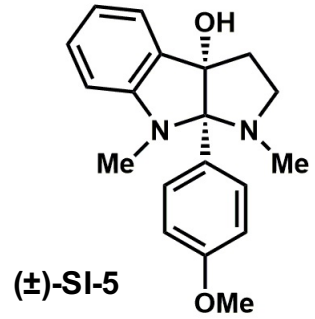
Parameter	Value
Title	JYS-3-99-F2-C2-aryl-OMe-rac.1.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	296.1
Pulse Sequence	zg30
Experiment	1D
Number of Scans	16
Receiver Gain	156.2
Relaxation Delay	1.0000
Pulse Width	12.5000
Acquisition Time	4.0894
Spectrometer Frequency	400.13
Spectral Width	8012.8
Nucleus	1H
Acquired Size	32768
Spectral Size	65536



Parameter	Value
Title	JYS-3-99-F2-C2-aryl-OMe-rac.2.fid
Origin	Bruker BioSpin GmbH
Solvent	CDCl3
Temperature	296.1
Pulse Sequence	zgpg30
Experiment	1D
Number of Scans	1024
Receiver Gain	72.0
Relaxation Delay	2.0000
Pulse Width	10.0000
Acquisition Time	1.3631
Spectrometer Frequency	100.62
Spectral Width	24038.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536



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